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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under 37 CFR 1.53 (c).

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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Philip	Jones	Italy
Vincenzo	Summa	Italy

☐ *Additional inventors are being named on the separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

HIV INTEGRASE INHIBITORS

CORRESPONDENCE ADDRESS

Direct all Correspondence to:
Merck & Co., Inc.
Patent Department - RY60-30
P.O. Box 2000
Rahway

☒ Customer Number 000210

STATE	New Jersey	ZIP CODE	07065	COUNTRY	U.S.A.

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Respectfully submitted,

SIGNATURE Kenneth R. Walton

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TYPED or PRINTED NAME Kenneth R. Walton

REGISTRATION NO. *(if appropriate)* 32,951

TELEPHONE 732 594 3462

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EXPRESS MAIL CERTIFICATE

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TITLE OF THE INVENTION
HIV INTEGRASE INHIBITORS

FIELD OF THE INVENTION

The present invention is directed to bicyclic pyridopyrazine- and pyrimidopyrazine-dione compounds and pharmaceutically acceptable salts thereof, their synthesis, and their use as inhibitors of the HIV integrase enzyme. The compounds and pharmaceutically acceptable salts thereof of the present invention are useful for preventing or treating infection by HIV and for preventing, treating or delaying the onset of AIDS.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the insertion by virally-encoded integrase of proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)]. All three enzymes have been shown to be essential for the replication of HIV.

It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhbitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The inhibition of integrase in vitro and HIV replication in cells is a direct result of inhibiting the strand transfer reaction catalyzed by the recombinant integrase in vitro in HIV infected

cells. The particular advantage of the present invention is highly specific inhibition of HIV integrase and HIV replication.

The following references are of interest as background:

US 6380249, US 6306891, and US 6262055 disclose 2,4-dioxobutyric acids and acid esters useful as HIV integrase inhibitors.

WO 01/00578 discloses 1-(aromatic- or heteroaromatic-substituted)-3-(heteroaromatic substituted)-1,3-propanediones useful as HIV integrase inhibitors.

US 2003/0055071 (corresponding to WO 02/30930), WO 02/30426, and WO 02/55079 each disclose certain 8-hydroxy-1,6-naphthyridine-7-carboxamides as HIV integrase inhibitors.

WO 02/036734 discloses certain aza- and polyaza-naphthalenyl ketones to be HIV integrase inhibitors.

WO 03/016275 discloses certain compounds having integrase inhibitory activity.

WO 03/35076 discloses certain 5,6-dihydroxypyrimidine-4-carboxamides as HIV integrase inhibitors, and WO 03/35077 discloses certain N-substituted 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamides as HIV integrase inhibitors.

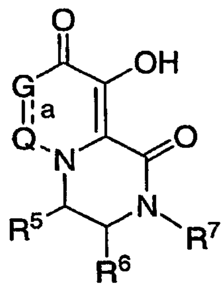
WO 03/062204 discloses certain hydroxynaphthyridinone carboxamides that are useful as HIV integrase inhibitors.

WO 04/004657 discloses certain hydroxypyrrole derivatives that are HIV integrase inhibitors.

SUMMARY OF THE INVENTION

The present invention is directed to bicyclic pyridopyrazine- and pyrimidopyrazine-dione compounds. These compounds are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the prevention, treatment, and delay in the onset of AIDS and/or ARC, either as compounds or their pharmaceutically acceptable salts or hydrates (when appropriate), or as pharmaceutical composition ingredients, whether or not in combination with other HIV/AIDS antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. More particularly, the present invention

includes compounds of Formula I, and pharmaceutically acceptable salts thereof:



(I)

wherein:

G is C-R^1, CH-R^1, N, or N-R^2;

Q is C-R^3, C-R^4, CH-R^3 or CH-R^4, with the proviso that (i) when G is C-R^1, then Q is C-R^3, (ii) when G is CH-R^1, then Q is CH-R^3, (iii) when G is N, then Q is C-R^4, and (iv) when G is N-R^2, then Q is CH-R^4;

bond "a" is a single bond or a double bond between G and Q, with the proviso that (i) when G is N or C-R^1, bond "a" is a double bond, and (ii) when G is CH-R^1 or N-R^2, bond "a" is a single bond;

R^1 is:

(1) H,

(2) halogen,

(3) C_{1-6} alkyl,

(4) C_{1-6} alkyl substituted with:

(a) -N(R^a)R^b,

(b) -N(R^a)-C(=O)-R^b,

(c) -N(R^a)-SO_2R^b,

(d) -N(R^a)-C_{1-6} alkylene-O-C_{1-6} alkyl,

(e) -N(R^a)-C(=O)-C(=O)-N(R^a)R^b,

(f) -OH,

(g) -HetD, or

(h) -N(R^a)-C_{1-6} alkylene-HetA,

(5) HetA,

(6) C(=O)-R^a,

(7) C(=O)-aryl, or

(8) C(=O)-HetA;

R^2 is H or C_{1-6} alkyl;

R^3 is:

(1) H,

(2) C_{1-6} alkyl, or

(3) C_{1-6} alkyl substituted with:

(a) -N(R^a)R^b,

(b) -N(R^a)-C(=O)-R^b,

(c) -N(R^a)-SO_2R^b,

(d) -N(R^a)-C_{1-6} alkylene-O-C_{1-6} alkyl,

(e) -N(R^a)-C(=O)-C(=O)-N(R^a)R^b,

(f) -HetD, or

(g) -N(R^a)-C_{1-6} alkylene-HetA, or

(4) C(=O)-C_{1-6} alkyl;

R^4 is:

(1) H,

(2) C_{1-6} alkyl, or

(3) C_{1-6} alkyl substituted with:

(a) -N(R^a)R^b,

(b) -N(R^a)-C(=O)-R^b,

(c) -N(R^a)-SO_2R^b,

(d) -N(R^a)-C_{1-6} alkylene-O-C_{1-6} alkyl,

(e) -N(R^a)-C(=O)-C(=O)-N(R^a)R^b,

(f) -HetD, or

(g) -N(R^a)-C_{1-6} alkylene-HetA;

R^5 and R^6 are each independently H or C_{1-6} alkyl;

R^7 is C_{1-6} alkyl substituted with T, wherein T is:

(A) aryl or aryl fused to a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the aryl or fused aryl is optionally substituted with from 1 to 5 substituents each of which is independently:

(1) $-C_{1-6}$ alkyl optionally substituted with -OH, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, -CN, $-NO_2$, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^a$, $-S(O)_nR^a$, $-SO_2N(R^a)R^b$, $-N(R^a)C(=O)R^b$, $-N(R^a)CO_2R^b$, $-N(R^a)SO_2R^b$, $-N(R^a)SO_2N(R^a)R^b$, $-OC(=O)N(R^a)R^b$, or $-N(R^a)C(=O)N(R^a)R^b$,

(2) $-O-C_{1-6}$ alkyl,

(3) $-C_{1-6}$ haloalkyl,

(4) $-O-C_{1-6}$ haloalkyl,

(5) -OH,

(6) halo,

(7) -CN,

(8) $-NO_2$,

(9) $-N(R^a)R^b$,

(10) $-C(=O)N(R^a)R^b$,

(11) $-C(=O)R^a$,

(12) $-CO_2R^a$,

(13) $-SR^a$,

(14) $-S(=O)R^a$,

(15) $-SO_2R^a$,

(16) $-SO_2N(R^a)R^b$,

(17) $-N(R^a)SO_2R^b$,

(18) $-N(R^a)SO_2N(R^a)R^b$,

(19) $-N(R^a)C(=O)R^b$,

(20) $-N(R^a)C(=O)-C(=O)N(R^a)R^b$,

(21) $-N(R^a)CO_2R^b$,

(22) phenyl,

(23) benzyl,

(24) -HetB,

(25) -C(=O)-HetB, or

(26) -HetC, or

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is

(i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, or hydroxy; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or $-C_{1-6}$ alkyl substituted with aryl;

each HetA is independently:

(A) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is:

(i) optionally substituted with from 1 to 4 substituents each of which is independently a $-C_{1-4}$ alkyl; and

(ii) optionally substituted with aryl or $-C_{1-4}$ alkylene-aryl; or

(B) a 9- or 10-membered aromatic heterobicyclic fused ring system containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the fused ring system consists of a 6-membered ring fused with either a 5-membered ring or another 6-membered ring, either ring of which is attached to the rest of the compound via a carbon atom; wherein the ring of the fused ring system attached to the rest of the compound via the carbon atom contains at least one of the heteroatoms; and wherein the fused ring system is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-4}$ alkyl; and

(ii) optionally substituted with aryl or $-C_{1-4}$ alkylene-aryl;

each HetB is independently a C_{4-7} azacycloalkyl or a C_{3-6} diazacycloalkyl, either of which is optionally substituted with from 1 to 4 substituents each of which is oxo or C_{1-6} alkyl;

each HetC is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halo, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, or hydroxy; or

each HetD is independently a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein any ring S atom is optionally oxidized to SO or SO_2, and wherein the heterocyclic ring is optionally fused with a benzene ring, and wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring, and wherein the heterocyclic ring is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-4}$ alkyl, $-C_{1-4}$ alkylene-$N(R^a)R^b$, or $-C(=O)OR^a$; and

(ii) optionally substituted with aryl, $-C_{1-4}$ alkylene-aryl, HetE, or $-C_{1-4}$ alkylene-HetE; wherein HetE is (i) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S or (ii) a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S;

each aryl is independently phenyl or naphthyl;

each R^a is independently H or C_{1-6} alkyl; and

each R^b is independently H or C_{1-6} alkyl.

The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating AIDS, methods of delaying the onset of AIDS, methods of preventing AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV.

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds of Formula I above, and pharmaceutically acceptable salts thereof. These compounds and pharmaceutically acceptable salts thereof are HIV integrase inhibitors.

A first embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is:

(1) H,

(2) halogen,

(3) C_{1-3} alkyl,

(4) C_{1-3} alkyl substituted with:

(a) $-N(R^a)R^b$,

(b) $-N(R^a)-C(=O)-R^b$,

(c) $-N(R^a)-SO_2R^b$,

(d) $-N(R^a)-C_{1-3}$ alkylene-O-C_{1-3} alkyl,

(e) $-N(R^a)-C(=O)-C(=O)-N(R^a)R^b$,

(f) -OH,

(g) -HetD, or

(h) $-N(R^a)-C_{1-3}$ alkylene-HetA,

(5) HetA,

(6) $C(=O)-R^a$,

(7) C(=O)-aryl, or

(8) C(=O)-HetA;

and all other variables are as originally defined (i.e., as defined in the Summary of the Invention).

A second embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is:

(1) H,

(2) C_{1-3} alkyl,

(3) chloro,

(4) bromo,

(5) $CH_2-N(R^a)R^b$,

(6) $CH(CH_3)-N(R^a)R^b$,

(7) $CH_2-N(R^a)-C(=O)-R^b$,

(8) $CH(CH_3)-N(R^a)-C(=O)-R^b$,

(9) $CH_2-N(R^a)-SO_2R^b$,

(10) $CH(CH_3)-N(R^a)-SO_2R^b$,

(11) $CH_2-N(R^a)-C_{1-3}$ alkylene-O-C_{1-3} alkyl,

(12) $CH(CH_3)-N(R^a)-C_{1-3}$ alkylene-O-C_{1-3} alkyl,

(13) $CH_2-N(R^a)-C(=O)-C(=O)-N(R^a)R^b$,

(14) $CH(CH_3)-N(R^a)-C(=O)-C(=O)-N(R^a)R^b$,

(15) CH_2OH,

(16) $CH(CH_3)OH$,

(17) CH_2-HetD,

(18) $CH(CH_3)$-HetD,
(19) CH_2-$N(R^a)$-CH_2-HetA,
(20) $CH(CH_3)$-$N(R^a)$-CH_2-HetA,
(21) HetA, or
(22) $C(=O)$-R^a;

and all other variables are as originally defined.

A third embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is:

(1) H,
(2) CH_3,
(3) chloro,
(4) bromo,
(5) CH_2-$NH(CH_3)$,
(6) CH_2-$N(CH_3)_2$,
(7) $CH(CH_3)$-$NH(CH_3)$,
(8) $CH(CH_3)$-$N(CH_3)_2$,
(9) $CH(CH_3)$-$NH(CH(CH_3)_2)$,
(10) CH_2-NH-$C(=O)CH_3$,
(11) CH_2-$N(CH_3)$-$C(=O)CH_3$,
(12) $CH(CH_3)$-NH-$C(=O)CH_3$,
(13) $CH(CH_3)$-$N(CH_3)$-$C(=O)CH_3$,
(14) CH_2-NH-SO_2CH_3,
(15) CH_2-$N(CH_3)$-SO_2CH_3,
(16) $CH(CH_3)$-NH-SO_2CH_3,
(17) $CH(CH_3)$-$N(CH_3)$-SO_2CH_3,
(18) CH_2-NH-$(CH_2)_{1-2}$-OCH_3,
(19) CH_2-$N(CH_3)$-$(CH_2)_{1-2}$-OCH_3,
(20) $CH(CH_3)$-NH-$(CH_2)_{1-2}$-OCH_3,
(21) $CH(CH_3)$-$N(CH_3)$-$(CH_2)_{1-2}$-OCH_3,
(22) CH_2-NH-$C(=O)$-$C(=O)$-$N(CH_3)_2$,
(23) CH_2-$N(CH_3)$-$C(=O)$-$C(=O)$-$N(CH_3)_2$,
(24) $CH(CH_3)$-NH-$C(=O)$-$C(=O)$-$N(CH_3)_2$,
(25) $CH(CH_3)$-$N(CH_3)$-$C(=O)$-$C(=O)$-$N(CH_3)_2$,
(26) CH_2OH,

(27) $CH(CH_3)OH$,

(28) CH_2-HetD,

(29) $CH(CH_3)$-HetD,

(30) CH_2-NH-CH_2-HetA,

(31) CH_2-N(CH_3)-CH_2-HetA,

(32) $CH(CH_3)$-NH-CH_2-HetA,

(33) $CH(CH_3)$-N(CH_3)-CH_2-HetA,

(34) HetA, or

(35) C(=O)-CH_3;

and all other variables are as originally defined.

A fourth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^2 is H or C_{1-3} alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A fifth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^2 is H or CH_3; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In an aspect of this embodiment, R^2 is H.

A sixth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^3 is H, C_{1-3} alkyl, or C(=O)-C_{1-3} alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A seventh embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^3 is H, CH_3, or C(=O)-CH_3; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In an aspect of this embodiment, R^3 is H or CH_3. In another aspect, R^3 is H.

An eighth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) H,

(2) C_{1-3} alkyl, or

(3) C_{1-3} alkyl substituted with:

(a) -N(R^a)R^b,

(b) -N(R^a)-C(=O)-R^b,

(c) -N(R^a)-SO_2R^b,

(d) -N(R^a)-C_{1-3} alkylene-O-C_{1-3} alkyl,

(e) -N(R^a)-C(=O)-C(=O)-N(R^a)R^b,

(f) -HetD, or

(g) $-N(R^a)-C_{1-3}$ alkylene-HetA;

and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A ninth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) H,

(2) C_{1-3} alkyl,

(3) $CH_2-N(R^a)R^b$,

(4) $CH(CH_3)-N(R^a)R^b$,

(5) $CH_2-N(R^a)-C(=O)-R^b$,

(6) $CH(CH_3)-N(R^a)-C(=O)-R^b$,

(7) CH_2-HetD, or

(8) $CH(CH_3)$-HetD.

and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A tenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) H,

(2) C_{1-3} alkyl,

(3) $CH_2-NH(CH_3)$,

(4) $CH(CH_3)-NH(CH_3)$,

(5) $CH_2-N(CH_3)_2$,

(6) $CH(CH_3)-N(CH_3)_2$,

(7) $CH_2-N(CH_3)-C(=O)-CH_3$,

(8) $CH(CH_3)-N(CH_3)-C(=O)-CH_3$, or

(9) CH_2-HetD;

and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An eleventh embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each independently H or C_{1-3} alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A twelfth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each independently H or CH_3; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A thirteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are both H; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A fourteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetA is:

(A) a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 3 heteroatoms independently selected from zero to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-3}$ alkyl; and

(ii) optionally substituted with phenyl or $-CH_2$-phenyl; or

(B) a 9- or 10-membered aromatic heterobicyclic fused ring system containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, zero or 1 O atoms, and zero or 1 S atoms; wherein the fused ring system consists of a 6-membered ring fused with either a 5-membered ring or another 6-membered ring, either ring of which is attached to the rest of the compound via a carbon atom; wherein the ring of the fused ring system attached to the rest of the compound via the carbon atom contains at least one of the heteroatoms; and wherein the fused ring system is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-3}$ alkyl; and

(ii) optionally substituted with phenyl or $-CH_2$-phenyl;

and all other variables are as originally defined or as defined in any one of the preceding embodiments.

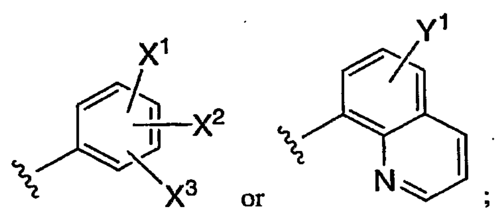
A fifteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetA is a heteroaromatic ring selected from the group consisting of oxadiazolyl, thiophenyl (alternatively referred to in the art as "thienyl"), pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridoimidazolyl; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is optionally substituted with methyl or phenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A sixteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetD is a 5- or 6-membered saturated heterocyclic ring containing a total of from 1 to 3 heteroatoms independently selected from 1 to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms, wherein any ring S atom is optionally oxidized to SO or SO_2, and wherein

the heterocyclic ring is optionally fused with a benzene ring, and wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring, and wherein the heterocyclic ring is: (i) optionally substituted with $-C_{1-3}$ alkyl, $-(CH_2)_{1-2}$-NH($-C_{1-3}$ alkyl), $-(CH_2)_{1-2}$-N($-C_{1-3}$ alkyl)$_2$ or -C(=O)O-C_{1-3} alkyl; and (ii) optionally substituted with phenyl, -CH_2-phenyl, HetE, or $-(CH_2)_{1-2}$-HetE; wherein HetE is (i) a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 3 heteroatoms independently selected from zero to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms or (ii) a 5- or 6-membered saturated heterocyclic ring containing a total of from 1 to 3 heteroatoms independently selected from 1 to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

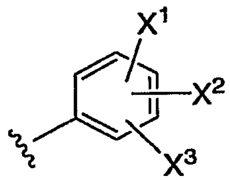
A seventeenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetD is a heterocyclic ring selected from the group consisting of pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, and piperidinyl fused with a benzene ring; wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An eighteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^7 is CH_2-T; and wherein T is:

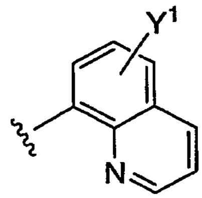


wherein X^1, X^2 and X^3 are each independently selected from the group consisting of -H, halo, $-C_{1-4}$ alkyl, -O-C_{1-4} alkyl, $-C_{1-4}$ fluoroalkyl, -SO_2-C_{1-4} alkyl, -C(=O)-NH($-C_{1-4}$ alkyl), -C(=O)-N($-C_{1-4}$ alkyl)$_2$, and HetC; Y^1 is -H, halo, $-C_{1-4}$ alkyl, or $-C_{1-4}$ fluoroalkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In an aspect of this embodiment, HetC in the definition of X^1, X^2 and X^3 is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-3}$ alkyl. In another aspect of this embodiment, HetC in the definition of X^1, X^2 and X^3 is selected from the group consisting of oxadiazolyl, thiophenyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridoimidazolyl; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is optionally substituted with methyl;

A nineteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^7 is CH_2-T; and wherein T is:



or



;

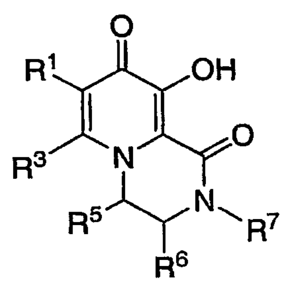
X^1 is fluoro, chloro, methyl, trifluoromethyl, methoxy, $-SO_2CH_3$, $-C(=O)-NH(CH_3)$, $-C(=O)-N(CH_3)_2$, or oxadiazolyl; X^2 and X^3 are each independently selected from the group consisting of -H, fluoro, chloro, methyl, trifluoromethyl, methoxy, $-SO_2CH_3$, $-C(=O)-NH(CH_3)$,and $-C(=O)-N(CH_3)_2$; Y^1 is -H, fluoro, chloro, methyl, or trifluoromethyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A twentieth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^7 is CH_2-T; and wherein T is 4-fluorophenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A twenty-first embodiment of the present invention is a compound of Formula I, wherein each R^a and R^b is independently H or C_{1-3} alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A twenty-second embodiment of the present invention is a compound of Formula I, wherein each R^a and R^b is independently H or methyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

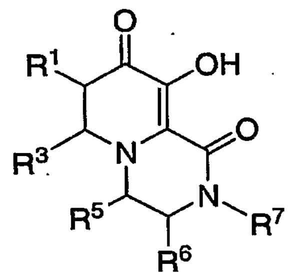
A first class of the present invention includes compounds of Formula IIa, and pharmaceutically acceptable salts thereof:



(IIa);

wherein R^1, R^3, R^5, R^6 and R^7 are each independently as originally defined above or as defined in any one of the foregoing embodiments.

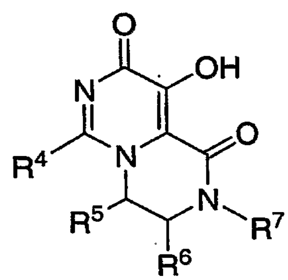
A second class of the present invention includes compounds of Formula IIa, and pharmaceutically acceptable salts thereof:



(IIb);

wherein R^1, R^3, R^5, R^6 and R^7 are each independently as originally defined above or as defined in any one of the foregoing embodiments.

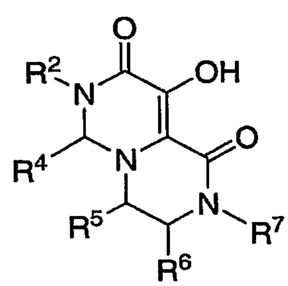
A third class of the present invention includes compounds of Formula IIIa, and pharmaceutically acceptable salts thereof:



(IIIa);

wherein R^4, R^5, R^6 and R^7 are each independently as originally defined above or as defined in any one of the foregoing embodiments.

A fourth class of the present invention includes compounds of Formula IIIb, and pharmaceutically acceptable salts thereof:



(IIIb);

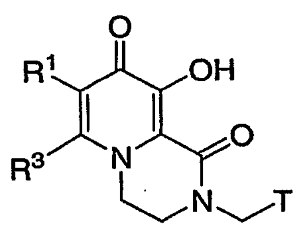
wherein R^2, R^4, R^5, R^6 and R^7 are each independently as originally defined above or as defined in any one of the foregoing embodiments.

A fifth class of the present invention includes compounds of Formula I, and pharmaceutically acceptable salts thereof, wherein R^1 is as defined in the first embodiment; R^2 is as defined in the fourth embodiment; R^3 is as defined in the sixth embodiment; R^4 is as defined in the eighth embodiment; R^5 and R^6 are as defined in the eleventh embodiment; HetA is as defined in the fourteenth embodiment; HetD is as defined in the sixteenth embodiment; R^a and R^b are as defined in the twenty-first embodiment; and all other variables are as originally defined above or as defined in any one of the foregoing embodiments.

A sub-class of the fifth class includes compounds of Formula I, and pharmaceutically acceptable salts thereof, wherein R^1 is as defined in the second embodiment; R^4 is as defined in the ninth embodiment; and all other variables are as defined in the fifth class.

A sixth class of the present invention includes compounds of Formula I, and pharmaceutically acceptable salts thereof, wherein R^1 is as defined in the third embodiment; R^2 is as defined in the fifth embodiment; R^3 is as defined in the seventh embodiment; R^4 is as defined in the tenth embodiment; R^5 and R^6 are as defined in the twelfth embodiment; HetA is as defined in the fifteenth embodiment; HetD is as defined in the seventeenth embodiment; R^a and R^b are as defined in the twenty-first embodiment; and all other variables are as originally defined above or as defined in any one of the foregoing embodiments.

A seventh class of the present invention includes compounds of Formula IV, and pharmaceutically acceptable salts thereof:



(IV)

wherein R^1 is:

(1) H,
(2) C_{1-3} alkyl,
(3) chloro,
(4) bromo,
(5) CH_2-N(R^a)R^b,
(6) $CH(CH_3)$-N(R^a)R^b,
(7) CH_2-N(R^a)-C(=O)-R^b,
(8) $CH(CH_3)$-N(R^a)-C(=O)-R^b,

(9) CH_2-N(R^a)-SO_2R^b,

(10) $CH(CH_3)$-N(R^a)-SO_2R^b,

(11) CH_2-N(R^a)-C_{1-3} alkylene-O-C_{1-3} alkyl,

(12) $CH(CH_3)$-N(R^a)-C_{1-3} alkylene-O-C_{1-3} alkyl,

(13) CH_2-N(R^a)-C(=O)-C(=O)-N(R^a)R^b,

(14) $CH(CH_3)$-N(R^a)-C(=O)-C(=O)-N(R^a)R^b,

(15) CH_2-OH,

(16) $CH(CH_3)$-OH,

(17) CH_2-HetD,

(18) $CH(CH_3)$-HetD,

(19) CH_2-N(R^a)-CH_2-HetA,

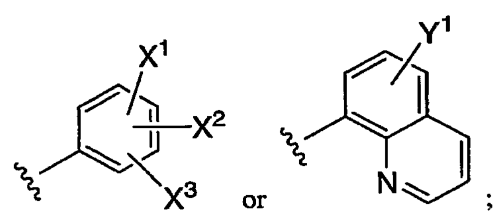
(20) $CH(CH_3)$-N(R^a)-CH_2-HetA,

(21) HetA, or

(22) C(=O)-R^a; and

R^3 is H, C_{1-3} alkyl, or C(=O)-C_{1-3} alkyl;

T is



wherein X^1, X^2 and X^3 are each independently selected from the group consisting of -H, halo, -C_{1-4} alkyl, -O-C_{1-4} alkyl, -C_{1-4} fluoroalkyl, -SO_2-C_{1-4} alkyl, -C(=O)-NH(-C_{1-4} alkyl), -C(=O)-N(-C_{1-4} alkyl)$_2$, and HetC;

Y^1 is -H, halo, -C_{1-4} alkyl, or -C_{1-4} fluoroalkyl;

HetA is a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 3 heteroatoms independently selected from zero to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the

heteroaromatic ring is (i) optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-3}$ alkyl and (ii) optionally substituted with phenyl or $-CH_2$-phenyl;

each HetC is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-3}$ alkyl;

HetD is a 5- or 6-membered saturated heterocyclic ring containing a total of from 1 to 3 heteroatoms independently selected from 1 to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms, wherein any ring S atom is optionally oxidized to SO or SO_2, and wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring, and wherein the heterocyclic ring is optionally substituted with $-C_{1-3}$ alkyl;

each R^a is independently H or C_{1-3} alkyl; and

R^b is H or C_{1-3} alkyl.

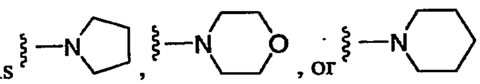
A sub-class of the seventh class includes compounds of Formula IV, and pharmaceutically acceptable salts thereof, wherein R^1 is:

(1) H,
(2) CH_3,
(3) bromo,
(4) $CH(CH_3)-N(R^a)R^b$,
(5) $CH(CH_3)-N(R^a)-C(=O)-R^b$,
(6) $CH(CH_3)-N(R^a)-SO_2R^b$,
(7) $CH(CH_3)-N(R^a)-C_{1-3}$ alkylene-O-C_{1-3} alkyl,
(8) $CH(CH_3)-N(R^a)-C(=O)-C(=O)-N(R^a)R^b$,
(9) $CH(CH_3)-OH$,
(10) $CH(CH_3)$-HetD,
(11) $CH(CH_3)-N(R^a)-CH_2$-HetA,
(12) HetA, or
(13) $C(=O)CH_3$; and

R^3 is H, CH_3, or $C(=O)-CH_3$;

T is 4-fluorophenyl;

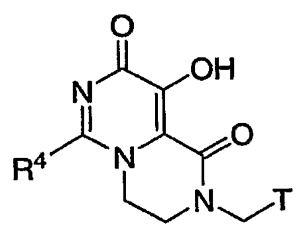
HetA is pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, or pyrazinyl;

HetD is  ;

R^a is H or CH_3; and

R^b is CH_3 or $CH(CH_3)_2$.

An eighth class of the present invention includes compounds of Formula V, and pharmaceutically acceptable salts thereof:

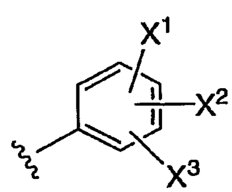


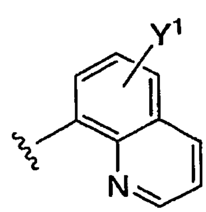
(V)

wherein R^4 is:

(1) H,
(2) $C_{1\text{-}3}$ alkyl,
(3) $CH_2\text{-}N(R^a)R^b$,
(4) $CH(CH_3)\text{-}N(R^a)R^b$,
(5) $CH_2\text{-}N(R^a)\text{-}C(=O)\text{-}R^b$,
(6) $CH(CH_3)\text{-}N(R^a)\text{-}C(=O)\text{-}R^b$,
(7) CH_2-HetD, or
(8) $CH(CH_3)$-HetD;

T is



or


;

wherein X^1, X^2 and X^3 are each independently selected from the group consisting of -H, halo, -C_{1-4} alkyl, -O-C_{1-4} alkyl, -C_{1-4} fluoroalkyl, -SO_2-C_{1-4} alkyl, -C(=O)-NH(-C_{1-4} alkyl), -C(=O)-N(-C_{1-4} alkyl)$_2$, and HetC;

Y^1 is -H, halo, -C_{1-4} alkyl, or -C_{1-4} fluoroalkyl;

each HetC is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently a -C_{1-3} alkyl;

HetD is a 5- or 6-membered saturated heterocyclic ring containing a total of from 1 to 3 heteroatoms independently selected from 1 to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms, wherein any ring S atom is optionally oxidized to SO or SO_2, and wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring, and wherein the heterocyclic ring is optionally substituted with -C_{1-3} alkyl;

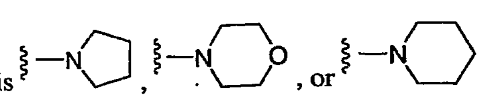
R^a is H or C_{1-3} alkyl; and

R^b is H or C_{1-3} alkyl.

A sub-class of the eighth class includes compounds of Formula V, and pharmaceutically acceptable salts thereof, wherein R^4 is:

(1) H,
(2) C_{1-3} alkyl,
(3) CH_2-N(R^a)R^b,
(4) CH(CH_3)-N(R^a)R^b,
(5) CH_2-N(R^a)-C(=O)-R^b,
(6) CH(CH_3)-N(R^a)-C(=O)-R^b,
(7) CH_2-HetD, or
(8) CH(CH_3)-HetD;

T is 4-fluorophenyl;

HetD is  ;

R^a is H or CH_3; and

R^b is CH_3.

Another embodiment of the present invention is a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of the compounds set forth in Table 1 below.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier.

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) an effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising an effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(e) A pharmaceutical combination which is (i) a compound of Formula I and (ii) an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents; wherein the compound of Formula I and the HIV infection/AIDS treatment agent are each employed in an amount that renders the combination effective for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS.

(f) The combination of (e), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

(g) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(h) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(i) The method of (h), wherein the compound of Formula (I) is administered in combination with an effective amount of at least one antiviral selected from the group consisting of HIV

protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(j) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(k) The method of (j), wherein the compound is administered in combination with an effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors

(l) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(m) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(n) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

The present invention also includes a compound of the present invention (i) for use in, (ii) for use as a medicament for, or (iii) for use in the preparation of a medicament for: (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS. In these uses, the compounds of the present invention can optionally be employed in combination with one or more HIV/AIDS treatment agents selected from HIV/AIDS antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(n) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt.

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, "C_{1-4} alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "alkylene" refers to any linear or branched chain alkylene group (or alternatively "alkanediyl") having a number of carbon atoms in the specified range. Thus, for example, "-C_{1-6} alkylene-" refers to any of the C_1 to C_6 linear or branched alkylenes. A class of alkylenes of particular interest with respect to the invention is -$(CH_2)_{1-6}$-, and sub-classes of particular interest include -$(CH_2)_{1-4}$-, -$(CH_2)_{1-3}$-, -$(CH_2)_{1-2}$-, and -CH_2-. Also of interest is the alkylene -$CH(CH_3)$-.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

The term "haloalkyl" refers to an alkyl group as defined above in which one or more of the hydrogen atoms has been replaced with a halogen (i.e., F, Cl, Br and/or I). Thus, for example, "C_{1-6} haloalkyl" (or "C_1-C_6 haloalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "fluoroalkyl" has an analogous meaning except that the halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series $(CH_2)_{0-4}CF_3$ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

The term "C_{4-7} azacycloalkyl" (or "C_4-C_7 azacycloalkyl") means a saturated cyclic ring consisting of one nitrogen and from four to seven carbon atoms (i.e., pyrrolidinyl, piperidinyl, azepanyl, or octahydroazocinyl).

The term "C_{3-6} diazacycloalkyl" (or "C_3-C_6 diazacycloalkyl") means a saturated cyclic ring consisting of two nitrogens and from three to six carbon atoms (e.g., imidazolidinyl, pyrazolidinyl, or piperazinyl).

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" means the ring can contain 1, 2, 3 or 4 heteroatoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range. Thus, for example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" is intended to include as aspects thereof, heterocyclic rings containing 2 to 4 heteroatoms, 3 or 4 heteroatoms, 1 to 3 heteroatoms, 2 or 3 heteroatoms, 1 or 2 heteroatoms, 1 heteroatom, 2 heteroatoms, and so forth.

When any variable (e.g., R^a or HetC) occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible provided that combinations result in stable compounds.

The term "substituted" (e.g., as in "is optionally substituted with from 1 to 5 substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed. Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (e.g., aryl, a

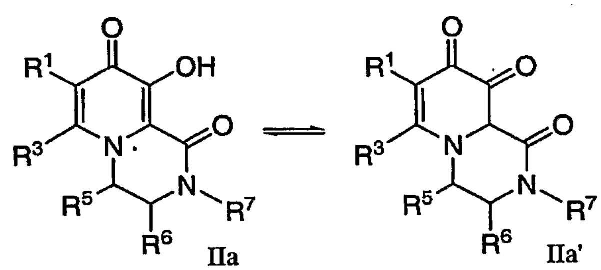
heteroaromatic ring, or a saturated heterocyclic ring) provided such ring substitution is chemically allowed and results in a stable compound.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject).

The symbol " ~~~ " in front of an open bond in the structural formula of a group marks the point of attachment of the group to the rest of the molecule.

When a compound of the present invention has one or more asymmetric centers and thus can occur as an optical isomer (e.g., an enantiomer or a diastereomer), it is understood that the present invention includes all isomeric forms of the compound, singly and in mixtures.

As would be recognized by one of ordinary skill in the art, certain of the compounds of the present invention can exist as tautomers, such as the following:


IIa IIa'

For the purposes of the present invention, a reference herein to a compound of Formula I (or IIa, IIb, IIIa, IIIb, IV or V) is a reference to compound I per se (or IIa, IIb, IIIa, IIIb, IV or V), to any one of its tautomers per se, or to mixtures thereof.

The compounds of the present inventions are useful in the inhibition of HIV integrase, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the prevention, treatment or the delay in the onset of consequent pathological conditions such as AIDS. Preventing AIDS, treating AIDS, delaying the onset of AIDS, or preventing or treating infection by HIV is defined as including, but not limited to, treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating

enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

Compounds representative of the present invention have been tested for inhibition in an assay for the strand transfer activity of integrase. The assay is conducted in the manner described in WO 02/30930. Representative compounds of the present invention exhibit inhibition of strand transfer activity in this assay. For example, the compounds set forth in Table 1 below were tested in the integrase assay and demonstrated IC_{50}'s of about 1 micromolar or less. Further description on conducting the assay using preassembled complexes is found in Hazuda et al., *J. Virol.* 1997, 71: 7005-7011; Hazuda et al., *Drug Design and Discovery* 1997, 15: 17-24; and Hazuda et al., *Science* 2000, 287: 646-650.

Compounds representative of the present invention have also been tested in an assay for inhibition of acute HIV infection of T-lymphoid cells, conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. For example, the compounds set forth below in Table 1 demonstrated IC_{95}'s of less than about 20 micromolar.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Many of the compounds of the invention carry an acidic moiety, in which case suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention mean providing the compound or a prodrug of the compound to the individual in need of treatment. When a compound of the invention or a prodrug thereof is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating HIV infection or AIDS), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or prodrug and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combining the specified ingredients in the specified amounts.

By “pharmaceutically acceptable” is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of the symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for prophylaxis of the symptoms of the disease or condition being prevented. The term also includes herein the amount of active compound sufficient to inhibit HIV integrase and thereby elicit the response being sought (i.e., an "inhibition effective amount"). When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

For the purpose of inhibiting HIV integrase, preventing or treating HIV infection or preventing, treating or delaying the onset of AIDS, the compounds of the present invention, optionally in the form of a salt, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders,

disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990.

The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

As noted above, the present invention is also directed to use of the HIV integrase inhibitor compounds of the present invention with one or more agents useful in the treatment of HIV infection or AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more HIV/AIDS antivirals, imunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS, such as those disclosed in Table 1 of WO 01/38332 or in the Table in WO 02/30930. Suitable HIV/AIDS antivirals for use in combination with the compounds of the present invention include, for example, HIV protease inhibitors (e.g., indinavir, atazanavir, lopinavir optionally with ritonavir, saquinavir, or nelfinavir), nucleoside HIV reverse transcriptase inhibitors (e.g., abacavir, lamivudine (3TC), zidovudine (AZT), or tenofovir), and non-nucleoside HIV reverse transcriptase inhibitors (e.g., efavirenz or nevirapine). It will be understood that the scope of combinations of the compounds of this invention with HIV/AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the foreogoing substances or to the list in the above-referenced Tables in WO 01/38332 and WO 02/30930, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS. The HIV/AIDS antivirals and other agents will typically be employed

in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the Physicians' Desk Reference, 57th edition, Thomson PDR, 2003. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

Abbreviations used in the instant specification, particularly the Schemes and Examples, include the following:

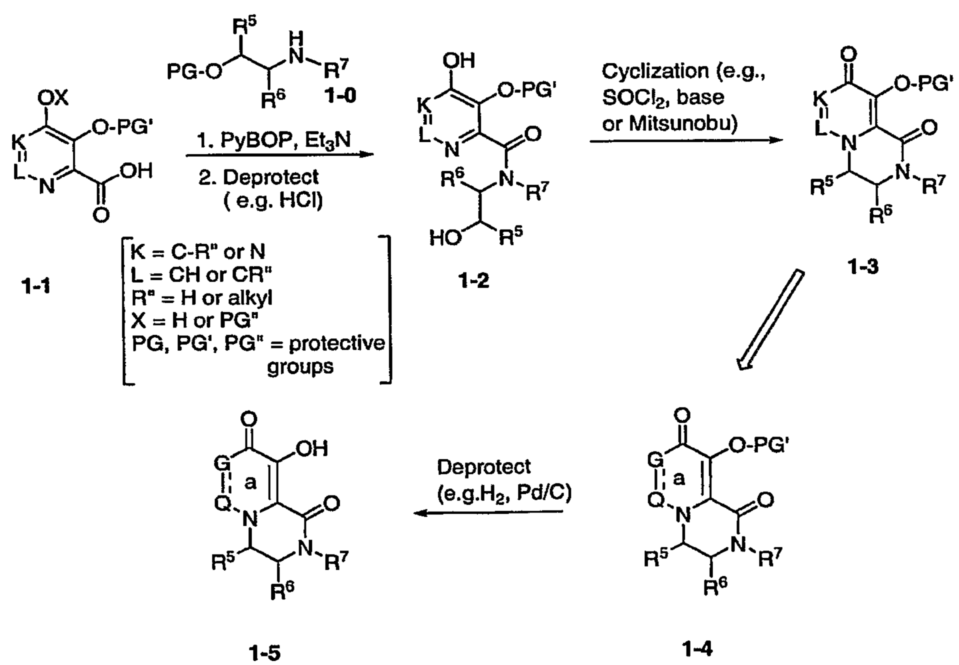
AIDS = acquired immunodeficiency syndrome
ARC = AIDS related complex
Bn = benzyl
BOP = benzotriazol-1-yloxytris-(dimethylamino)phosphonium
DCM = dichloromethane
DEAD = diethylazodicarboxylate
DMF = N,N-dimethylformamide
DMSO = dimethylsulfoxide
EDC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ES = electrospray
Et = ethyl
EtOH = ethanol
EtOAc = ethyl acetate
HIV = human immunodeficiency virus
HOBT or HOBt = 1-hydroxy benzotriazole hydrate
HPLC = high performance liquid chromatography
m-CPBA = meta-chloroperbenzoic acid
Me = methyl
MeOH = methanol
NIS = N-iodosuccinimide
NMR = nuclear magnetic resonance
Ph = phenyl
Py =pyridine
TBS = t- butyl-dimethylsilyl
TFA = trifluoroacetic acid
THF = tetrahydrofuran

The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting

materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

The general synthetic strategy for these compounds is outlined in Scheme 1. Essentially a functionalized heterocyclic carboxylic acid 1-1 (either a pyridine or a pyrimidine) is coupled with a secondary amine 1-0 bearing both a substituted benzyl group and a substituted protected 2-hydroxyethyl group. Once coupled, the protecting group(s) is/are removed to reveal a cyclization precursor 1-2. This key intermediate can be cyclized in a variety of conditions, such as by conversion of the hydroxyl to a suitable leaving group, (e.g. chloride) and then base mediated cyclization, or via a Mitsunobu process. These cyclizations give the crucial bicycle 1-3 which can be further synthetically elaborated to an analogue 1-4. Final deprotection yields the desired inhibitors 1-4 or 1-5.

Scheme 1

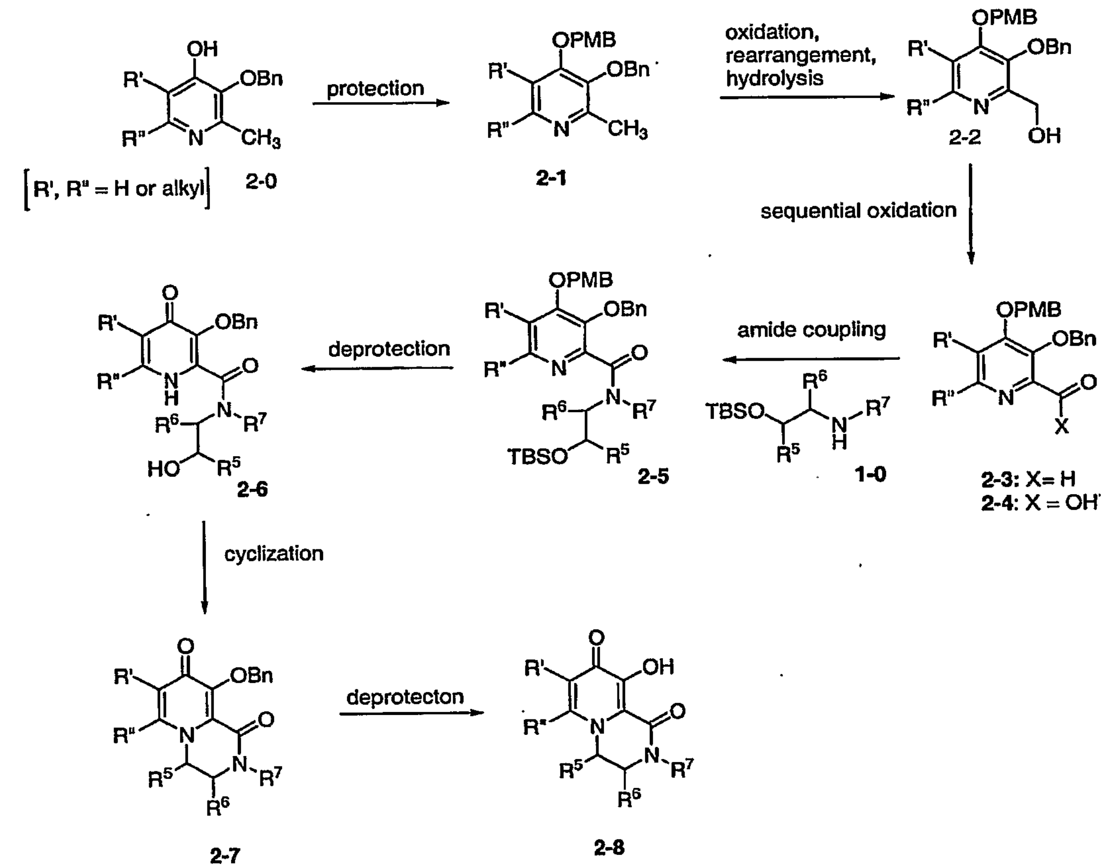


The key carboxylic acids or derivatives thereof employed as 1-1 in Scheme 1 can be readily obtained via established chemical processes (see, e.g., WO 02/06246; Sunderland et al. *Inorganic Chem.* 2001, 40: 6746; Piyamongkol et al., *Tetrahedron* 2001, 57: 3479; Boger, *J. Am. Chem. Soc.* 1999,

121: 2471; and Shimano, *Tetrahedron Lett.* 1998, 39: 4363). The secondary amines 1-0 can be readily prepared through alkylation processes (see, e.g., Michael B. Smith and Jerry March, Advanced Organic Chemistry, 5th edition, John Wiley & Sons, 2001, p. 499 and Richard Larock, Comprehensive Organic Transformations, VCH Publishers Inc., 1989 p. 397) or reductive aminations (see, e.g., R. O. Hutchins in Comprehensive Organic Synthesis, edited by B. M. Trost, Vol. 8, Pergamon Press, 1993, p. 25 and E. W. Baxter and A. B. Reitz, Organic Reactions, edited by L. E. Overman, Vol. 59, John Wiley, 2002, p. 1). Representative cyclization methods are described Seibel, *Bioorg. Med. Chem. Lett.* 2003, 13: 387; Mickelson et al., *J. Org. Chem.* 1995, 60: 4177; and Machon et al., *Farmaco Ed. Sci.* 1985, 40: 695-700. Suitable protecting groups and methods for removing them are described, for example, in T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Edition, Wiley-Interscience, 1999; and P. J. Kocienski, Protecting Groups, Thieme, 1994.

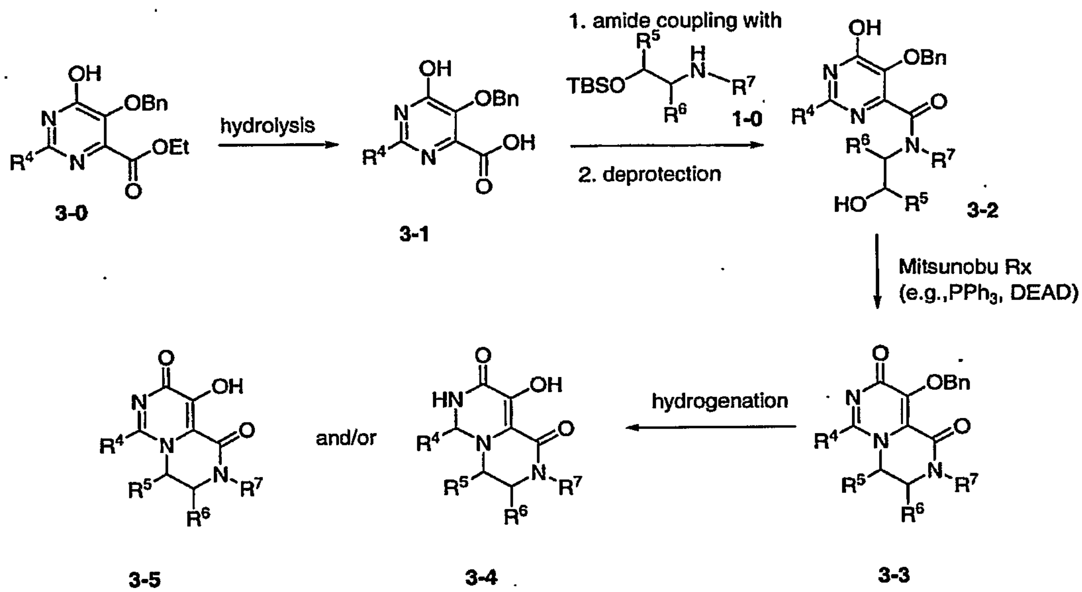
Schemes 2 to 8 below illustrate and expand upon the chemistry portrayed in Scheme 1. These schemes illustrate the chemistry In Scheme 2, a 3,4-dihydroxypyridine is differentially protected to give 2-1 (e.g., with benzyl and *p*-methoxybenzyl, although other protecting groups can be employed) and then *N*-oxidized and rearranged in a similar manner as described in *Tetrahedron* 2001, 57: 3479. After basic hydrolysis to the 2-hydroxymethyl compound 2-2, sequential oxidation (e.g., by Swern oxidation and then using sodium chlorite in the presence of sulfamic acid) will afford the aldehyde 2-3 and then the acid 2-4 (other suitable methods are described in M. Hudlicky, Oxidations in Organic Chemistry, Am. Chem. Soc., Washington, 1990). Amide coupling (e.g. with PyBOP) will give the amide 2-5 and the *tert*-butyldimethylsilyl and *para*-methoxybenzyl groups can then be removed from the alcohol (e.g., using acid although other deprotection methods are available) to give 2-6. Compund 2-6 can be cyclized by treatment with thionyl chloride in the presence of pyridine to afford the bicycle 2-7 (as described by Machon, Z. et al. *Farmaco Ed. Sci.*, 1985, 40(9), 695-700). The benzyl group can then be removed (e.g., by hydrogenolysis) to give 2-8.

Scheme 2



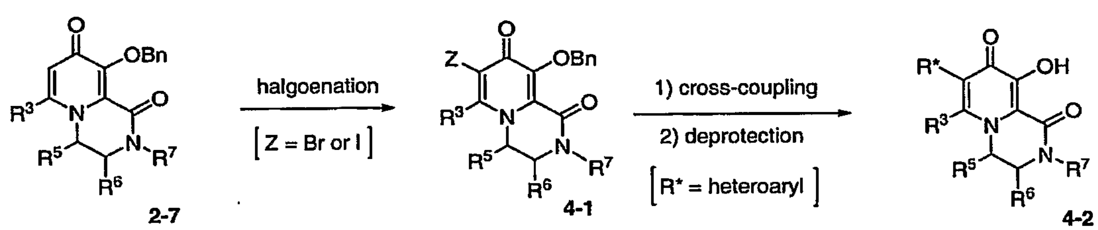
An alternative process for the preparation of these compounds is described in Scheme 3, where a suitable heterocyclic carboxylic ester 3-0 (synthesized as described, e.g., in Sunderland et al. *Inorganic Chem.* 2001, 40: 6746) can be hydrolyzed (e.g., KOH in EtOH with heating) to the acid 3-1, which can then be amide coupled (e.g., using PyBOP and Et3N) and deprotected (e.g., HCl in THF) to afford 3-2. This material can be cyclized under Mitsunobu conditions (e.g., as described by Seibel, *Bioorg. Med. Chem. Lett.* 2003, 13: 387; and Mickelson et al., *J. Org. Chem.* 1995, 60: 4177) to give the desired bicycle 3-3. Hydrogenation (e.g., H_2, Pd/C, MeOH) then gives structures of the type either 2-(benzyl)-9-hydroxy-6-alkyl-3,4-dihydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione 3-5 and/or 2-(benzyl)-9-hydroxy-6-alkyl-3,4,6,7-tetrahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione 3-4 depending on conditions used.

Scheme 3



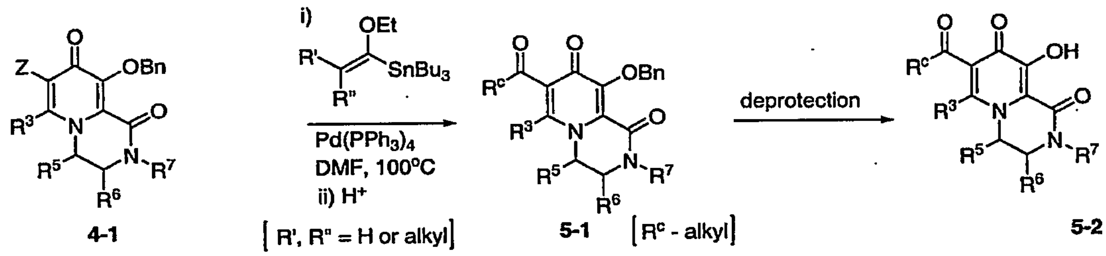
The core scaffold can be further manipulated as shown in Scheme 4. Halogenation (e.g., using NIS with mCPBA or using Br_2) can be performed to give the intermediate 4-1. This intermediate can then be cross-coupled (e.g., using a Stille reaction with an appropriate organostannane under Pd(0) catalysis as described in J. Tsuji, Palladium Reagents and Catalysts, Wiley, 1997, p. 228) to introduce a substituent at the C-7 position. Subsequent deprotection to remove benzyl will afford 4-2.

Scheme 4



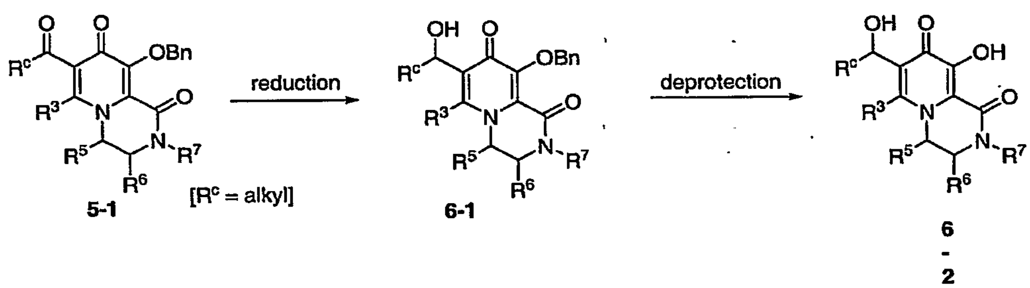
A modification of this procedure is depicted in Scheme 5 whereby the halogen intermediate 4-1 can be cross-coupled with a stannylated alkyl enol ether (see *Chemistry Lett.*1989, 1959-62). The resulting intermediate enol ether can then be hydrolyzed with acid to give the corresponding ketone 5-1, which can then be deprotected (e.g., HCl in THF with heating) to afford the compound 5-2.

Scheme 5



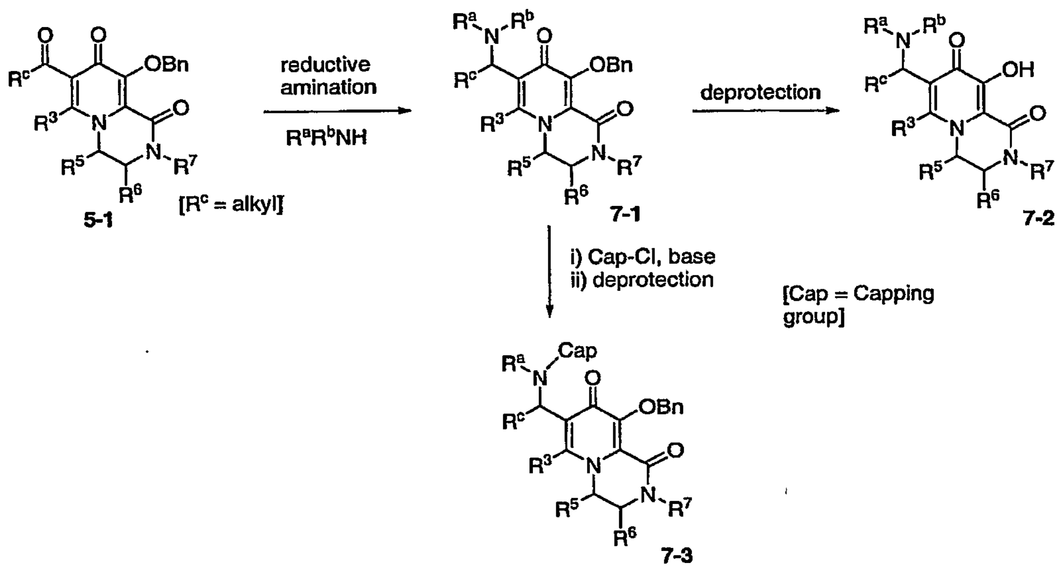
The ketone 5-1 can be readily transformed into the corresponding alcohol 6-1 as depicted in Scheme 6 using a suitable reducing agent (e.g., sodium borohydride or agents described in M. Hudlicky, Reductions in Organic Chemistry, A.C.S., Washington, 1996). Subsequent deprotection of 6-1 (e.g., H_2 with Pd/C) will then afford 6-2.

Scheme 6



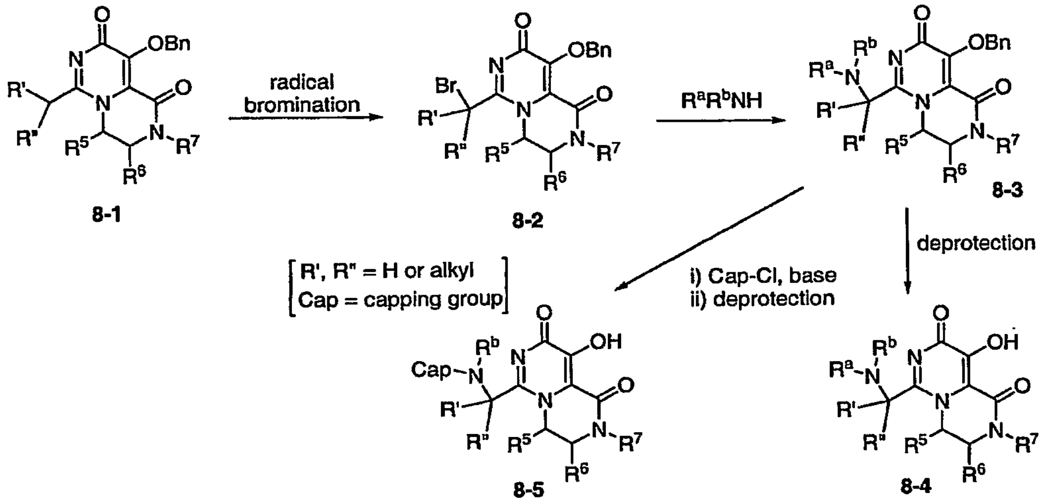
The ketone 5-1 can also be transformed into an amine 7-1 as described in Scheme 7 utilizing a reductive amination (e.g., treating 7-1 with excess amine in MeOH in the presence of sodium cyanoborohydride). Suitable reductive amination methods are described in, e.g., R. O. Hutchins in Comprehensive Organic Synthesis, edited by B. M. Trost, Pergamon Press, Vol. 8, 1993, p. 25 and E. W. Baxter and A. B. Reitz, Organic Reactions, edited by L. E. Overman, Vol. 59, John Wiley, 2002, p. 1. The amine 7-1 can then either be deprotected (e.g., by hydrogenation) to provide compound 7-2. The amine can also be further reacted with a capping group (Cap-Cl). Suitable capping groups include acyl chlorides, sulfonyl chlorides, and carbamyl chlorides and the like. Other acid derivatives in combination with an appropriate activating reagent (e.g., a carboxylic and coupling reagent such as EDC/HOBt or PyBOP) are suitable for use in this reaction. These reactions are conducted in the presence of a base (e.g., triethylamine) to scavenge the HCl by-product. Subsequent deprotection (e.g., H_2 with Pd/C) will then afford compound 7-3.

Scheme 7



An alternative method for functionalizing the core scaffold is depicted in Scheme 8, using the propensity of the carbon atom at the C-6 position of the bicycle to undergo radical bromination. Treatment of 8-1 with a brominating agent (e.g., *N*-bromosuccinimide in the presence of catalytic benzoyl peroxide) will afford the bromine derivative 8-2. The bromine can then be displaced by an amine (e.g., using chemistry described in, for example, Michael B. Smith and Jerry March, Advanced Organic Chemistry, 5th edition, John Wiley & Sons, 2001, p. 499 and in Richard Larock, Comprehensive Organic Transformations, VCH Publishers Inc, 1989, p.397) to afford 8-3. The amine can then either be deprotected (e.g., by hydrogenation) to give 8-4, or the amine can be further reacted with a capping group (Cap-Cl) in the manner described above in Scheme 7. Subsequent deprotection (e.g., H_2 with Pd/C) will then afford compound 8-5.

Scheme 8



The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

EXAMPLE 1

2-(4-Fluorobenzyl)-9-hydroxy-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione

Step 1: 3-(Benzyloxy)-4-[(4-methoxybenzyl)oxy]-2-methylpyridine (**A1**)

DEAD (1.5 equivalent) was added dropwise over 10 minutes to a stirred solution of 3-(benzyloxy)-2-methylpyridin-4-ol (1.0 equivalent), 4-methoxybenzylalcohol (1.3 equivalents) and triphenylphosphine (1.5 equivalents) in THF at room temperature. The mixture was stirred overnight and then the solvent was removed under reduced pressure. The resulting mixture was triturated with EtOAc and hexanes, and filtered. The solution was concentrated under reduced pressure and then purified by column chromatography on silica eluting with 100% EtOAc to yield the desired pyridine **A1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 5.6 Hz), 7.72-7.30 (7H, m), 6.96 (2H, d, J = 7.8 Hz), 6.83 (1H, d, J = 5.6 Hz), 5.15 (2H, s), 4.98 (2H, s), 3.74 (3H, s), 2.45 (3H, s). MS(ES) $C_{21}H_{21}NO_3$ requires: 335, found: 336 (M+H$^+$).

Step 2: {3-(Benzyloxy)-4-[(4-methoxybenzyl)oxy]pyridin-2-yl}methanol (**A2**)

mCPBA (2.0 equivalents) was added portionwise over 15 minutes to a stirred solution of the pyridine A1 (1.0 equivalent) in DCM at 0°C. The reaction was stirred overnight, gradually warming

to room temperature. The reaction mixture was then diluted with DCM and washed with 1 M NaOH solution (3 times), then brine and dried (Na_2SO_4). The desired pyridine-*N*-oxide was used without further purification. MS (ES) $C_{21}H_{21}NO_4$ requires: 351, found: 352 ($M+H^+$). The residue (1 equivalent) was taken up in excess Ac_2O, and the resulting mixture was heated at 130°C for 90 minutes. After cooling to room temperature, the mixture was concentrated under reduced pressure and was then taken up in DCM. The solution was washed with saturated $NaHCO_3$ solution and brine, and then dried (Na_2SO_4) prior to concentrating under reduced pressure. MS(ES) $C_{23}H_{23}NO_5$ requires: 393, found: 394 ($M+H^+$). The acetoxy derivative was taken up in MeOH and was treated with K_2CO_3 (1.5 equivalents). The mixture was stirred for 90 minutes and was then quenched by the addition of 6 M HCl solution. The MeOH was removed under reduced pressure and then more H_2O was added. The organics were extracted with DCM, and these DCM extracts were washed with brine and dried (Na_2SO_4). After concentrating under reduced pressure the desired alcohol **A2** was obtained. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, d, J = 5.6 Hz), 7.73-7.30 (10H, m), 6.89 (1H, d, J = 5.6 Hz), 5.23 (2H, s), 5.07 (2H, s), 4.67 (2H, s). MS(ES) $C_{21}H_{21}NO_4$ requires: 351, found: 352 ($M+H^+$).

<u>Step 3</u>: 3-(Benzyloxy)-4-[(4-methoxybenzyl)oxy]pyridine-2-carbaldehyde (**A3**)

Anhydrous DMSO (2.4 equivalents) was added dropwise over 10 minutes to a stirred solution of oxalyl chloride (1.2 equivalents) in dry DCM at -78°C under N_2. The resulting mixture was then stirred at this temperature for 5 minutes and a solution of the above alcohol **A2** (1 equivalent) in DCM was added dropwise over 10 minutes. After stirring for a further 30 minutes at -78°C, Et_3N (4.0 equivalents) was added dropwise over 5 minutes, the mixture was then stirred for 10 minutes and after the cooling bath was removed and the reaction was warmed to room temperature and stirred for an hour. After diluting with DCM, the mixture was washed with H_2O and then brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica eluting with 80% EtOAc/petroleum ether to yield the desired aldehyde **A3**. ^1H NMR (400 MHz, $CDCl_3$) δ 10.28 (1H, s), 8.44 (1H, d, J = 5.6 Hz), 7.45-7.30 (7H, m), 7.11 (1H, d, J = 5.6 Hz), 6.96 (2H, d, J = 7.8 Hz), 5.18 (2H, s), 5.15 (2H, s), 3.88 (3H, s). MS(ES) $C_{21}H_{19}NO_4$ requires: 349, found: 368 ($M+H_2O+H^+$).

<u>Step 4</u>: 3-(Benzyloxy)-4-[(4-methoxybenzyl)oxy]pyridine-2-carboxylic acid (**A4**)

Sulfamic acid (1.4 equivalents) and then sodium chlorite (1.1 equivalents) were added sequentially to a stirred solution of the aldehyde **A3** (1.0 equivalents) in acetone and water. The resulting mixture was stirred at room temperature for 30 minutes and then the acetone was removed under reduced pressure. The organics were extracted with DCM, and then the DCM extracts were washed with brine. The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield the desired acid **A4**.

^1H NMR (400 MHz, d_6-DMSO) δ 8.25 (1H, d, J = 5.6 Hz), 7.48-7.27 (8H, m), 6.97 (2H, d, J = 7.8 Hz), 5.24 (2H, s), 5.05 (2H, s), 3.78 (3H, s). MS(ES) $C_{21}H_{19}NO_5$ requires: 365, found: 366 ($M+H^+$).

Step 5: 3-(Benzyloxy)-*N*-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-*N*-(4-fluorobenzyl)-4-[(4-ethoxybenzyl)oxy]pyridine-2-carboxamide (**A5**)

PyBOP (1.2 equivalents) was added to a stirred solution of the acid **A4** (1.0 equivalent), (2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)(4-fluorobenzyl)amine (1.2 equivalents) [Prepared from 4-fluorobenzylamine and 2-{[*tert*-butyl(dimethyl)silyl]-oxy}ethanal with $NaBH_4$ in MeOH] and Et_3N (1.5 equivalents) in DCM and the mixture was stirred at room temperature overnight. The reaction was diluted with DCM and washed sequentially with 0.5 N HCl solution, saturated $NaHCO_3$ solution and brine and then dried (Na_2SO_4). The resulting solution was concentrated under reduced pressure and then purified by column chromatography on silica eluting with 50-60% EtOAc/petroleum ether to yield the desired amide **A5**. MS (ES) $C_{36}H_{43}FN_2O_5Si$ requires: 630, found: 631 ($M+H^+$).

Step 6: 3-(Benzyloxy)-*N*-(4-fluorobenzyl)-*N*-(2-hydroxyethyl)-4-oxo-1,4-dihydropyridine-2-carboxamide (**A6**)

The amide **A5** (1 equivalent) was taken up in THF and treated with 3.5 N HCl solution (7 equivalents). The resulting solution was stirred overnight and then was neutralized with solid NaOH. The THF was removed under reduced pressure and the organics were then extracted with DCM. The combined organic extracts were dried and concentrated under reduced pressure. The residue purified by column chromatography on silica eluting with 10-20% MeOH/DCM to yield the desired alcohol **A6**. MS(ES) $C_{22}H_{21}FN_2O_4$ requires: 396, found: 397 ($M+H^+$).

Step 7: 9-(Benzyloxy)-2-(4-fluorobenzyl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**A7**)

A mixture of the above alcohol **A6** (1 equivalent), thionyl chloride (5 equivalents), and pyridine (10 equivalents) in $CHCl_3$ were heated at reflux for 8 hours. Further thionyl chloride (3.5 equivalents), and pyridine (10 equivalents) were added and heating was continued for a further 2 hours. The reaction was cooled to room temperature and was diluted with DCM. The mixture was washed with 1 N NaOH solution, H_2O and brine. After drying (Na_2SO_4) the mixture was concentrated under reduced pressure and purified by column chromatography on silica eluting with 10% MeOH/DCM to yield the desired bicycle **A7**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (2H, d, J = 7.4 Hz), 7.45-7.27 (5H, m), 7.11 (1H, d, J = 7.4 Hz), 7.07 (2H, t, J = 8.4 Hz), 6.44 (1H, d, J = 7.4 Hz), 5.37 (2H, s), 4.66 (2H, s), 3.88 (2H, t, J = 5.3 Hz), 3.45 (2H, t, J = 5.3 Hz). MS (ES) $C_{22}H_{19}FN_2O_3$ requires: 378, found: 379 ($M+H^+$).

Step 8: 2-(4-Fluorobenzyl)-9-hydroxy-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**A8**)

10% Pd on carbon was added to a stirred solution of the bicycle **A7** (1 equivalent) in MeOH containing 1 M HCl solution (1.5 equivalents) and then after degassing the reaction vessel an H_2 atmosphere was introduced and the reaction was stirred for 90 minutes. The catalyst was filtered off through celite and the filter pad washed well with MeOH. The organics were concentrated under reduced pressure and the residue was purified by reverse phase HPLC to yield the desired bicycle **A8**. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.88 (1H, d, J = 7.0 Hz), 7.45 (2H, dd, J = 8.5, 5.5 Hz), 7.19 (2H, t, J = 8.5 Hz), 6.57 (1H, d, J = 7.0 Hz), 4.73 (2H, s), 4.33 (2H, t, J = 5.5 Hz), 3.75 (2H, t, J = 5.5 Hz). MS(ES) $C_{15}H_{13}FN_2O_3$ requires: 288, found: 289 (M+H$^+$).

EXAMPLE 2

2-(4-Fluorobenzyl)-9-hydroxy-7-pyridin-3-yl-3,4-dihydro-2*H*-pyrido [1,2-*a*]pyrazine-1,8-dione

Step 1: 9-(Benzyloxy)-2-(4-fluorobenzyl)-7-iodo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**B1**)

To a solution of the bicycle **A7** (1 equivalent) in MeOH at 70°C was added *N*-iodo-succinimide (4 equivalents) and then mCPBA (4 equivalent). The mixture was then heated at 75°C for 3 hours and was subsequently concentrated under reduced pressure. The residue was taken up in DCM and washed with sodium sulfite solution and 0.5 N NaOH solution. The mixture was dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude iodide **B1**. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.46 (1H, s), 7.53 (2H, d, J = 6.6 Hz), 7.44-7.27 (5H, m), 7.19 (2H, t, J = 8.9 Hz), 5.09 (2H, s), 4.67 (2H, s), 4.18 (2H, t, J = 5.5 Hz), 3.13 (2H, t, J = 5.5 Hz). MS(ES) $C_{22}H_{18}FIN_2O_3$ requires: 504, found: 505 (M+H$^+$).

Step 2: 2-(4-Fluorobenzyl)-9-hydroxy-7-pyridin-3-yl-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**B2**)

A mixture of the iodide **B1** (1 equivalent) and 3-pyridyltributylstannane (3 equivalents) and $Pd(PPh_3)_4$ (10 mol%) in DMF was heated at 100°C for 2 hours under N_2. The solvent was removed under reduced pressure whilst azeotroping with xylene. MS (ES) $C_{27}H_{22}FN_3O_3$ requires: 455, found: 456 (M+H$^+$). The residue was taken up in THF and treated with 6 N HCl; this mixture was heated at 60°C for 4 hours and was subsequently freeze dried and purified by reverse phase HPLC to yield the desired pyridine **B2**. ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.39 (1H, s), 8.78 (1H, d, J = 6.0 Hz), 8.38 (1H, s), 7.98 (1H, t, J = 6.2 Hz), 7.47 (2H, dd, J = 8.5, 5.5 Hz), 7.22 (2H, t, J = 8.5 Hz), 6.57 (1H, d, J = 7.0 Hz), 4.76

(2H, s), 4.33 (2H, t, $J = 5.5$ Hz), 3.75 (2H, t, $J = 5.5$ Hz). MS(ES) $C_{20}H_{16}FN_3O_3$ requires: 365, found: 366 ($M+H^+$).

EXAMPLE 3

7-Acetyl-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione

Step 1: 7-Acetyl-9-(benzyloxy)-2-(4-fluorobenzyl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**C1**)

The iodide **B1** (1 equivalent) was cross-coupled with 2-ethoxyvinyltributyl stannane as described in Example 2 Step 1. The crude residue, obtained after azeotroping with xylene, was taken up in THF and treated with 0.5 M HCl at room temperature for 30 minutes. The solution was neutralized with 1 N NaOH solution and extracted with DCM. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was then purified by column chromatography on silica eluting with 100% EtOAc to yield the desired ketone **C1**. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.77-7.01 (9H, m), 5.43 (2H, s), 4.73 (2H, s), 4.04 (2H, t, $J = 5.5$ Hz), 3.52 (2H, t, $J = 5.5$ Hz), 2.77 (3H, s). MS(ES) $C_{24}H_{21}FN_2O_4$ requires: 420, found: 421 ($M+H^+$).

Step 2: 7-Acetyl-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**C2**)

The ketone **C1** (1 equivalent) was taken up in THF and treated with 6 N HCl; this mixture was heated at 60°C for 4 hours and was then concentrated under reduced pressure and purified by reverse phase HPLC to yield the desired bicycle **C2**. ^1H NMR (300 MHz, d_6-DMSO) δ 12.40 (1H, br. s), 8.17 (1H, s), 7.44 (2H, dd, $J = 8.7, 5.8$ Hz), 7.18 (2H, t, $J = 8.7$ Hz), 4.72 (2H, s), 4.33 (2H, t, $J = 5.5$ Hz), 3.72 (2H, t, $J = 5.5$ Hz), 2.57 (3H, s). MS(ES) $C_{17}H_{15}FN_2O_4$ requires: 330, found: 331 ($M+H^+$).

EXAMPLE 4

2-(4-Fluorobenzyl)-9-hydroxy-7-(1-hydroxyethyl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione

Step 1: 9-(Benzyloxy)-2-(4-fluorobenzyl)-7-(1-hydroxyethyl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**D1**)

Sodium borohydride (1 equivalent) was added to a stirred solution of the **C1** (1 equivalent) in EtOH and the resulting mixture was stirred at room temperature for 45 minutes. The reaction was quenched with NH_4Cl solution was added and the solvent was removed under reduced pressure. H_2O was added and then the organics were extracted with DCM. The organic extracts were

dried (Na_2SO_4), and concentrated under reduced pressure to yield the alcohol **D1**. MS(ES) $C_{24}H_{23}N_2O_4F$ requires: 422, found: 423 ($M+H^+$).

Step 2: 2-(4-Fluorobenzyl)-9-hydroxy-7-(1-hydroxyethyl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**D2**)

The bicycle **D1** was deprotected in accordance with the procedure described in Example 1 Step 8 to yield **D2** after reverse phase HPLC. ^1H NMR (300 MHz, d_6-DMSO) δ 7.87 (1H, s), 7.47 (2H, dd, J = 8.6, 5.5 Hz), 7.26 (2H, t, J = 8.6 Hz), 4.92 (1H, q, J = 6.4 Hz), 4.87 (2H, s), 4.42 (2H, t, J = 5.5 Hz), 3.77 (2H, t, J = 5.5 Hz), 1.35 (3H, d, J = 6.4 Hz). MS(ES) $C_{17}H_{17}N_2O_4F$ requires: 332, found: 333 ($M+H^+$).

EXAMPLE 5

2-(4-Fluorobenzyl)-9-hydroxy-7-[1-(methylamino)ethyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione

Step 1: 9-(Benzyloxy)-2-(4-fluorobenzyl)-7-[1-(methylamino)ethyl]-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**E1**)

Sodium cyanoborohydride (6 equivalents) was added to a stirred solution of methylamine.HCl (10 equivalents) and the ketone **C1** (1 equivalent) in MeOH and the mixture was stirred at room temperature overnight. The mixture was quenched by the addition of NH_4Cl solution and 1 M NaOH. The MeOH was removed under reduced pressure and the organics were then extracted with DCM, dried (Na_2SO_4) and concentrated under reduced pressure. MS(ES) $C_{25}H_{26}FN_3O_3$ requires: 435, found: 436 ($M+H^+$).

Step 2: 2-(4-Fluorobenzyl)-9-hydroxy-7-[1-(methylamino)ethyl]-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**E2**)

The bicycle **E1** was deprotected as described in Example 1 step 8 to yield **E2**, as the TFA salt, after reverse phase HPLC. ^1H NMR (300 MHz, d_6-DMSO) δ 12.25 (1H, br. s), 8.85 (1H, br. s), 8.70 (1H, br. s), 7.87 (1H, s), 7.47 (2H, dd, J = 8.8, 5.7 Hz), 7.26 (2H, t, J = 8.8 Hz), 4.73 (2H, s), 4.38-4.24 (3H, m), 3.77 (2H, t, J = 5.5 Hz), 2.44 (3H, t, J = 4.9 Hz), 1.55 (3H, d, J = 6.8 Hz). MS(ES) $C_{18}H_{20}N_3O_3F$ requires: 345, found: 346 ($M+H^+$).

EXAMPLE 6

N-{1-[2-(4-Fluorobenzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrazin-7-yl]ethyl}-*N*-methylacetamide

Step 1: *N*-{1-[2-(4-Fluorobenzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrazin-7-yl]ethyl}-*N*-methylacetamide **(F1)**

Ac_2O (3 equivalents) was added to a stirred solution of the crude amine **E1** (1 equivalent) and Et_3N (3 equivalents) in DCM and the resulting mixture was stirred at room temperature for 1 hour. More DCM was added and the mixture was washed with saturated aqueous $NaHCO_3$ solution, and brine. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography on silica eluting with 3-6 % MeOH/DCM to yield the desired acetamide **F1**. MS(ES) $C_{27}H_{28}FN_3O_4$ requires: 477, found: 478 ($M+H^+$). The intermediate was deprotected as described in Example 1 step 8 to yield **F2** after reverse phase HPLC. ^1H NMR (400 MHz, d_6-DMSO) Major Rotamer: δ 7.83 (1H, s), 7.47-7.35 (2H, m), 7.19 (2H, t, *J* = 8.6 Hz), 5.18 (1H, q, *J* = 7.0 Hz), 4.80-4.65 (2H, m), 4.30-4.18 (2H, m), 3.78-3.65 (2H, m), 2.78 (3H, s), 2.29 (3H, s), 1.38 (3H, d, *J* = 7.0 Hz). MS(ES) $C_{20}H_{22}N_3O_4F$ requires: 387, found: 388 ($M+H^+$).

EXAMPLE 7

2-(4-Fluorobenzyl)-9-hydroxy-6-methyl-3,4,6,7-tetrahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione and 2-(4-Fluorobenzyl)-9-hydroxy-6-methyl-3,4-dihydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione

Step 1: 5-(Benzyloxy)-6-hydroxy-2-methylpyrimidine-4-carboxylic acid **(G1)**

A solution of ethyl 5-(benzyloxy)-6-hydroxy-2-methylpyrimidine-4-carboxylate (1 equivalent) [*Inorganic Chem.* 2001, 40, 6746] in MeOH was treated with KOH (3.4 equivalents) and the mixture was heated at reflux of 90 minutes. The reaction was quenched by the addition of 6 M HCl solution and the solvent was removed under reduced pressure. The organics were dissolved in 5 % MeOH/DCM and were dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield the acid **G1**. ^1H NMR (400 MHz, d_6-DMSO) δ 7.45-7.30 (5H, m), 5.13 (2H, s), 2.29 (3H, s). MS (ES) $C_{13}H_{12}N_2O_4$ requires: 260, found: 261 ($M+H^+$).

Step 2: 5-(Benzyloxy)-*N*-(4-fluorobenzyl)-6-hydroxy-*N*-(2-hydroxyethyl)-2-methylpyrimidine-4-carboxamide **(G2)**

The acid **G1** was coupled with (2-{[*tert*-butyl(dimethyl)silyl]-oxy}ethyl)(4-fluorobenzyl)amine via the procedure described in Example 1 Step 5 to yield after purification by

column chromatography on silica eluting with 100% EtOAc to yield the desired amide. MS (ES) $C_{28}H_{36}FN_3O_4Si$ requires: 525, found: 526 ($M+H^+$). The intermediate was taken up in THF and treated with 1 M HCl (1.5 equivalents). After stirring at room temperature for 1 hour the reaction was quenched by the addition of 1 M NaOH solution. The organics were extracted with DCM, dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography on silica eluting with 5% MeOH/DCM yielded the desired alcohol **G2**. ^{1}H NMR (400 MHz, d_6-DMSO) Major Rotamer: δ 7.48-7.30 (7H, m), 6.95 (2H, t, J = 8.5 Hz), 5.15 (2H, s), 4.73 (2H, s), 3.48-3.37 (2H, m), 3.15-3.00 (2H, m) 2.29 (3H, s). MS (ES) $C_{22}H_{22}FN_3O_4$ requires: 411, found: 412 ($M+H^+$).

<u>Step 3</u>: 9-(Benzyloxy)-2-(4-fluorobenzyl)-6-methyl-3,4-dihydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione (**G3**)

DEAD (1.5 equivalent) was added dropwise over 10 minutes to a stirred solution of the alcohol **G2** (1.0 equivalent) and triphenylphosphine (1.5 equivalents) in DCM at room temperature. The mixture was stirred for 90 minutes and then the solvent was removed under reduced pressure whilst dry loading onto silica. The desired bicycle was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield **G3**. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.51 (2H, d, J = 6.6 Hz), 7.43-7.31 (5H, m), 7.18 (2H, t, J = 8.8 Hz), 5.09 (2H, s), 4.67 (2H, s), 4.07-3.97 (2H, m), 3.60-3.52 (2H, m) 2.37 (3H, s). MS (ES) $C_{22}H_{20}FN_3O_3$ requires: 393, found: 394 ($M+H^+$).

<u>Step 4</u>: 2-(4-Fluorobenzyl)-9-hydroxy-6-methyl-3,4-dihydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione (**G5**) and 2-(4-fluorobenzyl)-9-hydroxy-6-methyl-3,4,6,7-tetrahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione (**G4**)

The bicycle **G3** was deprotected in the manner described in Example 1 Step 8, except that acid was not present, to yield after reverse phase HPLC, eluted first **G5** and then **G4**.

Spectra for **G5**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.44 (2H, dd, J = 5.7, 8.6 Hz), 7.18 (2H, t, J = 8.6 Hz), 4.73 (2H, s), 4.32 (2H, t, J = 5.5 Hz), 3.68 (2H, t, J = 5.5 Hz), 2.45 (3H, s). MS (ES) $C_{15}H_{14}FN_3O_3$ requires: 303, found: 304 ($M+H^+$).

Spectra for **G4**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.08 (1H, br. s), 8.09 (1H, s), 7.34 (2H, dd, J = 5.7, 8.6 Hz), 7.16 (2H, t, J = 8.6 Hz), 4.63 (1H, d, J = 8.8 Hz), 4.58 (1H, d, J = 8.8 Hz), 4.23 (1H, q, J = 8.8 Hz), 3.56-3.32 (2H, m), 3.16-3.07 (1H, m), 2.78-2.66 (1H, m), 1.26 (3H, d, J = 6.0 Hz). MS (ES) $C_{15}H_{16}FN_3O_3$ requires: 305, found: 306 ($M+H^+$).

EXAMPLE 8

2-(4-Fluorobenzyl)-9-hydroxy-6-(morpholin-4-ylmethyl)-3,4-dihydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione

Step 1: 2-(4-Fluorobenzyl)-9-hydroxy-6-(morpholin-4-ylmethyl)-3,4-dihydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione (**H1**)

A solution of the bicycle **G3** (1 equivalent) and freshly recrystallized *N*-bromo-succinimide (1.4 equivalents) in DMF was treated with catalytic benzoyl peroxide and the mixture was heated at 70°C for 40 minutes to yield the bromo-derivative. MS (ES) $C_{22}H_{19}BrFN_3O_3$ requires: 471, found: 472 (M+H$^+$). Morpholine (10 equivalents) was added to the reaction mixture and the temperature was raised to 90°C for 40 minutes. The solvent was removed under reduced pressure whilst azeotroping with xylene. MS (ES) $C_{26}H_{27}FN_4O_4$ requires: 478, found: 479 (M+H$^+$). The crude residue was deprotected as described in Example 1 step 8 to yield the desired amine **H1** after reverse phase HPLC purification. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.22 (1H, br. s), 7.47 (2H, dd, *J* = 8.5, 5.7 Hz), 7.25 (2H, t, J = 8.5 Hz), 4.78 (2H, s), 4.25-4.18 (4H, m), 3.84-3.60 (8H, m), 3.15-2.90 (2H, m). MS (ES) $C_{19}H_{21}FN_4O_4$ requires: 388, found: 389 (M+H$^+$).

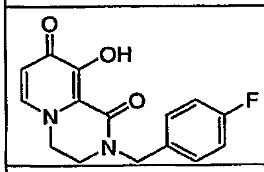
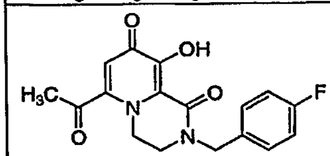
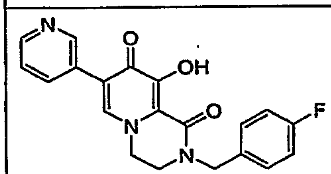
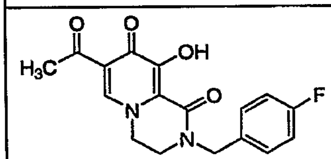
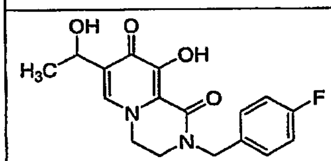
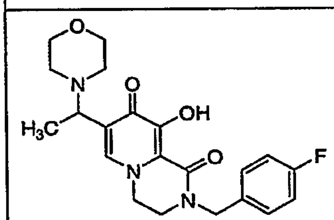
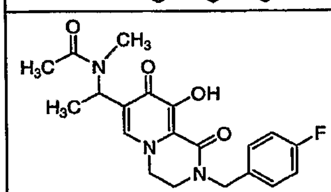
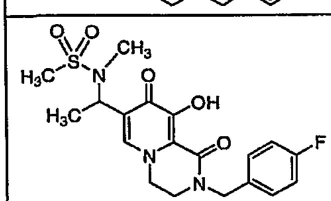
EXAMPLE 9

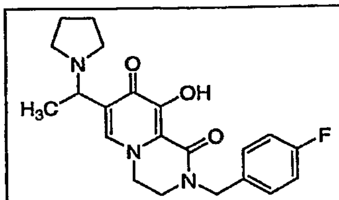
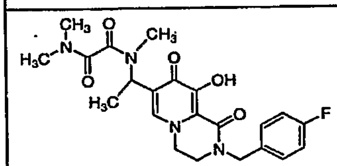
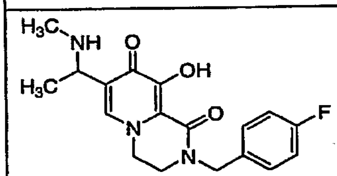
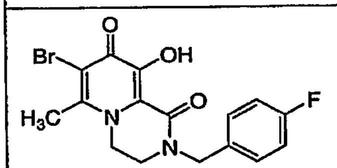
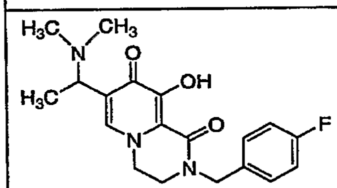
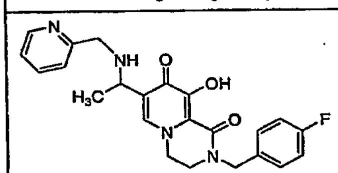
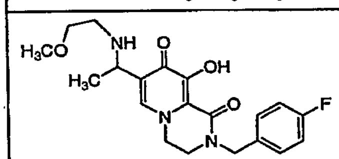
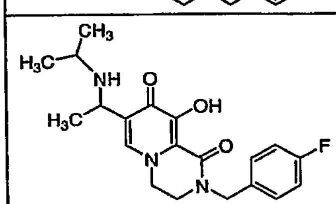
7-Bromo-2-(4-fluorobenzyl)-9-hydroxy-6-methyl-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione

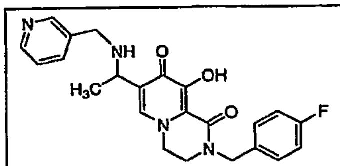
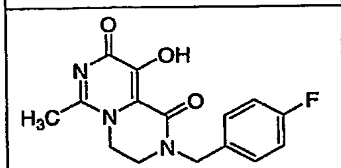
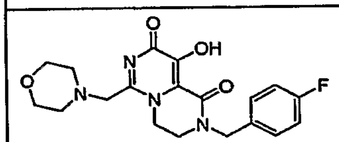
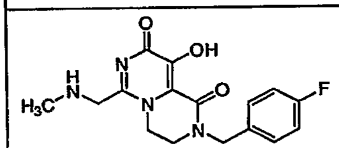
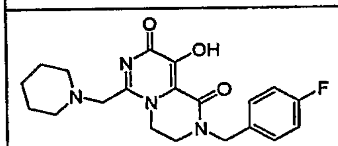
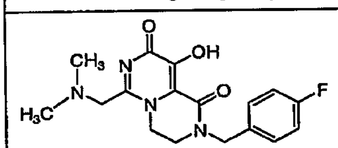
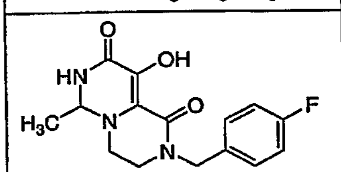
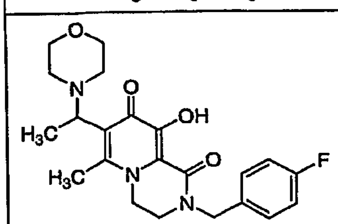
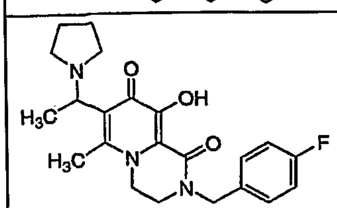
Step 1: 7-Bromo-2-(4-fluorobenzyl)-9-hydroxy-6-methyl-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione (**I1**)

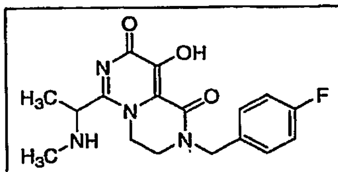
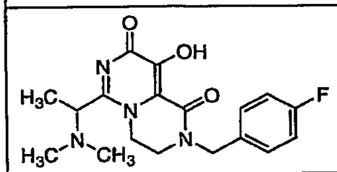
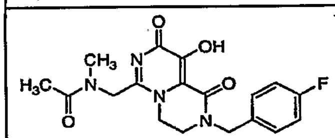
To a solution of 9-(benzyloxy)-2-(4-fluorobenzyl)-6-methyl-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,8-dione the bicycle **I0** (1 equivalent) [Prepared in a similar manner to Example 1] in DCM was treated with bromine (2 equivalents) and stirred at room temperature for 24 hours. The reaction was concentrated under reduced pressure and the residue was purified by reverse phase HPLC to yield the desired bicycle **I1**. ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.48 (1H, dd, *J* = 8.6, 5.5 Hz), 7.26 (2H, t, *J* = 8.6 Hz), 4.79 (2H, s), 4.30 (2H, t, *J* = 5.4 Hz), 3.75 (2H, t, *J* = 5.4 Hz), 2.61 (3H, s). MS(ES) $C_{16}H_{14}BrFN_2O_3$ requires: 380, found: 381 (M+H$^+$).

Table 1 below lists compounds of the present invention. The table provides the structure and name of each compound, the mass of its molecular ion plus 1 (M+) or molecular ion minus 1 (M-) as determined via ES, and a reference to the preparative example that is, or is representative of, the procedure employed to prepare the compound.

Structure	Name	Ex.	M+H+
	2-(4-Fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	1	289
	6-Acetyl-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	1	331
	2-(4-Fluorobenzyl)-9-hydroxy-7-pyridin-3-yl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	2	366
	7-Acetyl-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	3	331
	2-(4-Fluorobenzyl)-9-hydroxy-7-(1-hydroxyethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	4	333
	2-(4-Fluorobenzyl)-9-hydroxy-7-(1-morpholin-4-ylethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	5	402
	N-{1-[2-(4-Fluorobenzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazin-7-yl]ethyl}-N-methylacetamide	6	388
	N-{1-[2-(4-Fluorobenzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazin-7-yl]ethyl}-N-methylmethane-sulfonamide	6	424

	2-(4-Fluorobenzyl)-9-hydroxy-7-(1-pyrrolidin-1-ylethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	5	386
	N-{1-[2-(4-Fluorobenzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetra-hydro-2H-pyrido[1,2-a]pyrazin-7-yl]ethyl}-N,N',N'-trimethylethane-diamide	6	445
	2-(4-Fluorobenzyl)-9-hydroxy-7-[1-(methylamino)ethyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	5	346
	7-Bromo-2-(4-fluorobenzyl)-9-hydroxy-6-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	9	381
	7-[1-(Dimethylamino)ethyl]-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	5	360
	2-(4-Fluorobenzyl)-9-hydroxy-7-{1-[(pyridin-2-ylmethyl)amino]ethyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	5	423
	2-(4-Fluorobenzyl)-9-hydroxy-7-{1-[(2-methoxyethyl)amino]ethyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	5	390
	2-(4-Fluorobenzyl)-9-hydroxy-7-[1-(isopropylamino)ethyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	5	374

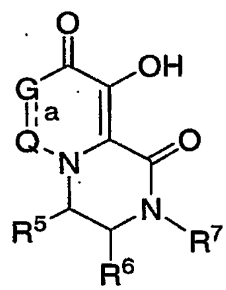
	2-(4-Fluorobenzyl)-9-hydroxy-7-{1-[(pyridin-3-ylmethyl)amino]ethyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	5	423
	2-(4-Fluorobenzyl)-9-hydroxy-6-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione	7	304
	2-(4-Fluorobenzyl)-9-hydroxy-6-(morpholin-4-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione	8	389
	2-(4-Fluorobenzyl)-9-hydroxy-6-[(methylamino)methyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione	8	333
	2-(4-Fluorobenzyl)-9-hydroxy-6-(piperidin-1-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione	8	387
	6-[(Dimethylamino)methyl]-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione	8	347
	2-(4-Fluorobenzyl)-9-hydroxy-6-methyl-3,4,6,7-tetrahydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione	7	306
	2-(4-fluorobenzyl)-9-hydroxy-6-methyl-7-(1-morpholin-4-ylethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	5	416
	2-(4-fluorobenzyl)-9-hydroxy-6-methyl-7-(1-pyrrolidin-1-ylethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione	5	400

	2-(4-fluorobenzyl)-9-hydroxy-6-[1-(methylamino)ethyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione	8	347
	6-[1-(dimethylamino)ethyl]-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione	8	361
	N-{[2-(4-fluorobenzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrazino[1,2-c]pyrimidin-6-yl]methyl}-N-methylacetamide	8	375

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

G is C-R^1, CH-R^1, N, or N-R^2;

Q is C-R^3, C-R^4, CH-R^3 or CH-R^4, with the proviso that (i) when G is C-R^1, then Q is C-R^3, (ii) when G is CH-R^1, then Q is CH-R^3, (iii) when G is N, then Q is C-R^4, and (iv) when G is N-R^2, then Q is CH-R^4;

bond "a" is a single bond or a double bond between G and Q, with the proviso that (i) when G is N or C-R^1, bond "a" is a double bond, and (ii) when G is CH-R^1 or N-R^2, bond "a" is a single bond;

R^1 is:

(1) H,
(2) halogen,
(3) C_{1-6} alkyl,
(4) C_{1-6} alkyl substituted with:
  (a) -N(R^a)R^b,
  (b) -N(R^a)-C(=O)-R^b,
  (c) -N(R^a)-SO_2R^b,
  (d) -N(R^a)-C_{1-6} alkylene-O-C_{1-6} alkyl,
  (e) -N(R^a)-C(=O)-C(=O)-N(R^a)R^b,
  (f) -OH,
  (g) -HetD, or

(h) -N(R^a)-C_{1-6} alkylene-HetA,

(5) HetA,

(6) C(=O)-R^a,

(7) C(=O)-aryl, or

(8) C(=O)-HetA;

R^2 is H or C_{1-6} alkyl;

R^3 is:

(1) H,

(2) C_{1-6} alkyl, or

(3) C_{1-6} alkyl substituted with:

(a) -N(R^a)R^b,

(b) -N(R^a)-C(=O)-R^b,

(c) -N(R^a)-SO_2R^b,

(d) -N(R^a)-C_{1-6} alkylene-O-C_{1-6} alkyl,

(e) -N(R^a)-C(=O)-C(=O)-N(R^a)R^b,

(f) -HetD, or

(g) -N(R^a)-C_{1-6} alkylene-HetA, or

(4) C(=O)-C_{1-6} alkyl;

R^4 is:

(1) H,

(2) C_{1-6} alkyl, or

(3) C_{1-6} alkyl substituted with:

(a) -N(R^a)R^b,

(b) -N(R^a)-C(=O)-R^b,

(c) -N(R^a)-SO_2R^b,

(d) -N(R^a)-C_{1-6} alkylene-O-C_{1-6} alkyl,

(e) -N(R^a)-C(=O)-C(=O)-N(R^a)R^b,

(f) -HetD, or

(g) -N(R^a)-C_{1-6} alkylene-HetA;

R^5 and R^6 are each independently H or C_{1-6} alkyl;

R^7 is C_{1-6} alkyl substituted with T, wherein T is:

(A) aryl or aryl fused to a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the aryl or fused aryl is optionally substituted with from 1 to 5 substituents each of which is independently:

(1) $-C_{1-6}$ alkyl optionally substituted with -OH, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, -CN, $-NO_2$, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^a$, $-S(O)_nR^a$, $-SO_2N(R^a)R^b$, $-N(R^a)C(=O)R^b$, $-N(R^a)CO_2R^b$, $-N(R^a)SO_2R^b$, $-N(R^a)SO_2N(R^a)R^b$, $-OC(=O)N(R^a)R^b$, or $-N(R^a)C(=O)N(R^a)R^b$,

(2) $-O-C_{1-6}$ alkyl,

(3) $-C_{1-6}$ haloalkyl,

(4) $-O-C_{1-6}$ haloalkyl,

(5) -OH,

(6) halo,

(7) -CN,

(8) $-NO_2$,

(9) $-N(R^a)R^b$,

(10) $-C(=O)N(R^a)R^b$,

(11) $-C(=O)R^a$,

(12) $-CO_2R^a$,

(13) $-SR^a$,

(14) $-S(=O)R^a$,

(15) $-SO_2R^a$,

(16) $-SO_2N(R^a)R^b$,

(17) $-N(R^a)SO_2R^b$,

(18) $-N(R^a)SO_2N(R^a)R^b$,

(19) $-N(R^a)C(=O)R^b$,

(20) $-N(R^a)C(=O)-C(=O)N(R^a)R^b$,

(21) $-N(R^a)CO_2R^b$,

(22) phenyl,

(23) benzyl,

(24) -HetB,

(25) -C(=O)-HetB, or

(26) -HetC, or

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is

(i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or -C_{1-6} alkyl substituted with aryl;

each HetA is independently:

(A) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a -C_{1-4} alkyl; and

(ii) optionally substituted with aryl or -C_{1-4} alkylene-aryl; or

(B) a 9- or 10-membered aromatic heterobicyclic fused ring system containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the fused ring system consists of a 6-membered ring fused with either a 5-membered ring or another 6-membered ring, either ring of which is attached to the rest of the compound via a carbon atom; wherein the ring of the fused ring system attached to the rest of the compound via the carbon atom contains at least one of the heteroatoms; and wherein the fused ring system is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a -C_{1-4} alkyl; and

(ii) optionally substituted with aryl or -C_{1-4} alkylene-aryl;

each HetB is independently a C_{4-7} azacycloalkyl or a C_{3-6} diazacycloalkyl, either of which is optionally substituted with from 1 to 4 substituents each of which is oxo or C_{1-6} alkyl;

each HetC is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halo, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; or

each HetD is independently a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein any ring S atom is optionally oxidized to SO or SO_2, and wherein the heterocyclic ring is optionally fused with a benzene ring, and wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring, and wherein the heterocyclic ring is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-4}$ alkyl, $-C_{1-4}$ alkylene-$N(R^a)R^b$, or $-C(=O)OR^a$; and

(ii) optionally substituted with aryl, $-C_{1-4}$ alkylene-aryl, HetE, or $-C_{1-4}$ alkylene-HetE; wherein HetE is (i) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S or (ii) a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S;

each aryl is independently phenyl or naphthyl;

each R^a is independently H or C_{1-6} alkyl; and

each R^b is independently H or C_{1-6} alkyl.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^1 is:

(1) H,

(2) halogen,

(3) C_{1-3} alkyl,

(4) C_{1-3} alkyl substituted with:

(a) $-N(R^a)R^b$,

(b) $-N(R^a)-C(=O)-R^b$,

(c) $-N(R^a)-SO_2R^b$,

(d) $-N(R^a)-C_{1-3}$ alkylene-O-C_{1-3} alkyl,

(e) $-N(R^a)-C(=O)-C(=O)-N(R^a)R^b$,

(f) -OH,

(g) -HetD, or

(h) $-N(R^a)-C_{1-3}$ alkylene-HetA,

(5) HetA,

(6) $C(=O)-R^a$,

(7) C(=O)-aryl, or

(8) C(=O)-HetA;

R^2 is H or C_{1-3} alkyl;

R^3 is H, C_{1-3} alkyl, or $C(=O)-C_{1-3}$ alkyl;

R^4 is:

(1) H,

(2) C_{1-3} alkyl, or

(3) C_{1-3} alkyl substituted with:

(a) $-N(R^a)R^b$,

(b) $-N(R^a)-C(=O)-R^b$,

(c) $-N(R^a)-SO_2R^b$,

(d) $-N(R^a)-C_{1-3}$ alkylene-O-C_{1-3} alkyl,

(e) $-N(R^a)-C(=O)-C(=O)-N(R^a)R^b$,

(f) -HetD, or

(g) $-N(R^a)-C_{1-3}$ alkylene-HetA;

R^5 and R^6 are each independently H or C_{1-3} alkyl;

HetA is:

(A) a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 3 heteroatoms independently selected from zero to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-3}$ alkyl; and

(ii) optionally substituted with phenyl or $-CH_2$-phenyl; or

(B) a 9- or 10-membered aromatic heterobicyclic fused ring system containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, zero or 1 O atoms, and zero or 1 S atoms; wherein the fused ring system consists of a 6-membered ring fused with either a 5-membered ring or another 6-membered ring, either ring of which is attached to the rest of the compound via a carbon atom; wherein the ring of the fused ring system attached to the rest of the compound via the carbon atom contains at least one of the heteroatoms; and wherein the fused ring system is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-3}$ alkyl; and

(ii) optionally substituted with phenyl or $-CH_2$-phenyl; and

HetD is a 5- or 6-membered saturated heterocyclic ring containing a total of from 1 to 3 heteroatoms independently selected from 1 to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms, wherein any ring S atom is optionally oxidized to SO or SO_2, and wherein the heterocyclic ring is optionally fused with a benzene ring, and wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring, and wherein the heterocyclic ring is:

(i) optionally substituted with $-C_{1-3}$ alkyl, $-(CH_2)_{1-2}-NH(-C_{1-3}$ alkyl), $-(CH_2)_{1-2}-N(-C_{1-3}$ alkyl$)_2$ or $-C(=O)O-C_{1-3}$ alkyl; and

(ii) optionally substituted with phenyl, $-CH_2$-phenyl, HetE, or $-(CH_2)_{1-2}$-HetE; wherein HetE is (i) a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 3 heteroatoms independently selected from zero to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms or (ii) a 5- or 6-membered saturated heterocyclic ring containing a total of from 1 to 3 heteroatoms independently selected from 1 to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms;

each R^a is independently H or C_{1-3} alkyl; and

R^b is H or C_{1-3} alkyl.

3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^1 is:

(1) H,
(2) C_{1-3} alkyl,
(3) chloro,
(4) bromo,
(5) CH_2-N(R^a)R^b,
(6) CH(CH_3)-N(R^a)R^b,
(7) CH_2-N(R^a)-C(=O)-R^b,
(8) CH(CH_3)-N(R^a)-C(=O)-R^b,
(9) CH_2-N(R^a)-SO_2R^b,
(10) CH(CH_3)-N(R^a)-SO_2R^b,
(11) CH_2-N(R^a)-C_{1-3} alkylene-O-C_{1-3} alkyl,
(12) CH(CH_3)-N(R^a)-C_{1-3} alkylene-O-C_{1-3} alkyl,
(13) CH_2-N(R^a)-C(=O)-C(=O)-N(R^a)R^b,
(14) CH(CH_3)-N(R^a)-C(=O)-C(=O)-N(R^a)R^b,
(15) CH_2OH,
(16) CH(CH_3)OH,
(17) CH_2-HetD,
(18) CH(CH_3)-HetD,
(19) CH_2-N(R^a)-CH_2-HetA,
(20) CH(CH_3)-N(R^a)-CH_2-HetA,
(21) HetA, or
(22) C(=O)-R^a; and

R^4 is:

(1) H,
(2) C_{1-3} alkyl,
(3) CH_2-N(R^a)R^b,
(4) CH(CH_3)-N(R^a)R^b,
(5) CH_2-N(R^a)-C(=O)-R^b,
(6) CH(CH_3)-N(R^a)-C(=O)-R^b,
(7) CH_2-HetD, or
(8) CH(CH_3)-HetD.

4. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein

R^1 is:

(1) H,
(2) CH_3,
(3) chloro,
(4) bromo,
(5) CH_2-NH(CH_3),
(6) CH_2-N(CH_3)$_2$,
(7) CH(CH_3)-NH(CH_3),
(8) CH(CH_3)-N(CH_3)$_2$,
(9) CH(CH_3)-NH(CH(CH_3)$_2$),
(10) CH_2-NH-C(=O)CH_3,
(11) CH_2-N(CH_3)-C(=O)CH_3,
(12) CH(CH_3)-NH-C(=O)CH_3,
(13) CH(CH_3)-N(CH_3)-C(=O)CH_3,
(14) CH_2-NH-SO_2CH_3,
(15) CH_2-N(CH_3)-SO_2CH_3,
(16) CH(CH_3)-NH-SO_2CH_3,
(17) CH(CH_3)-N(CH_3)-SO_2CH_3,
(18) CH_2-NH-(CH_2)$_{1\text{-}2}$-OCH_3,
(19) CH_2-N(CH_3)-(CH_2)$_{1\text{-}2}$-OCH_3,
(20) CH(CH_3)-NH-(CH_2)$_{1\text{-}2}$-OCH_3,
(21) CH(CH_3)-N(CH_3)-(CH_2)$_{1\text{-}2}$-OCH_3,
(22) CH_2-NH-C(=O)-C(=O)-N(CH_3)$_2$,
(23) CH_2-N(CH_3)-C(=O)-C(=O)-N(CH_3)$_2$,
(24) CH(CH_3)-NH-C(=O)-C(=O)-N(CH_3)$_2$,
(25) CH(CH_3)-N(CH_3)-C(=O)-C(=O)-N(CH_3)$_2$,
(26) CH_2OH,
(27) CH(CH_3)OH,
(28) CH_2-HetD,
(29) CH(CH_3)-HetD,
(30) CH_2-NH-CH_2-HetA,

(31) CH_2-N(CH_3)-CH_2-HetA,
(32) CH(CH_3)-NH-CH_2-HetA,
(33) CH(CH_3)-N(CH_3)-CH_2-HetA,
(34) HetA, or
(35) C(=O)-CH_3;

R^2 is H or CH_3;

R^3 is H, CH_3, or C(=O)-CH_3;

R^4 is:

(1) H,
(2) C_{1-3} alkyl,
(3) CH_2-NH(CH_3),
(4) CH(CH_3)-NH(CH_3),
(5) CH_2-N(CH_3)$_2$,
(6) CH(CH_3)-N(CH_3)$_2$,
(7) CH_2-N(CH_3)-C(=O)-CH_3,
(8) CH(CH_3)-N(CH_3)-C(=O)-CH_3, or
(9) CH_2-HetD;

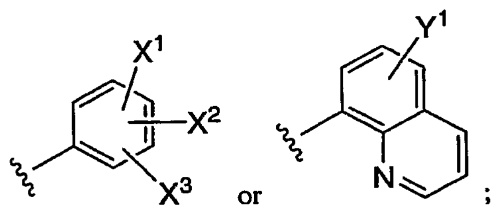
R^5 and R^6 are each independently H or CH_3;

HetA is a heteroaromatic ring selected from the group consisting of oxadiazolyl, thiophenyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridoimidazolyl; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is optionally substituted with methyl or phenyl; and

HetD is a heterocyclic ring selected from the group consisting of pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, and piperidinyl fused with a benzene ring; wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring.

5. The compound according to claim 1, or a pharmaceutically acceptable salt

thereof, wherein R^7 is CH_2-T; wherein T is:



wherein X^1, X^2 and X^3 are each independently selected from the group consisting of -H, halo, -C_{1-4} alkyl, -O-C_{1-4} alkyl, -C_{1-4} fluoroalkyl, -SO_2-C_{1-4} alkyl, -C(=O)-NH(-C_{1-4} alkyl), -C(=O)-N(-C_{1-4} alkyl)$_2$, and HetC; and

Y^1 is -H, halo, -C_{1-4} alkyl, or -C_{1-4} fluoroalkyl.

6. The compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein X^1 is fluoro, chloro, methyl, trifluoromethyl, methoxy, -SO_2CH_3, -C(=O)-NH(CH_3), -C(=O)-N(CH_3)$_2$, or oxadiazolyl;

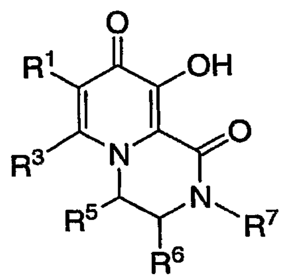
X^2 and X^3 are each independently selected from the group consisting of -H, fluoro, chloro, methyl, trifluoromethyl, methoxy, -SO_2CH_3, -C(=O)-NH(CH_3),and -C(=O)-N(CH_3)$_2$; and

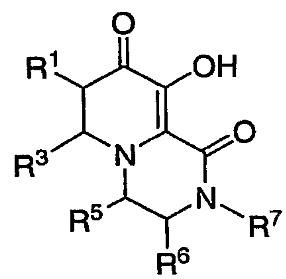
Y^1 is -H, fluoro, chloro, methyl, or trifluoromethyl.

7. The compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein T is 4-fluorophenyl.

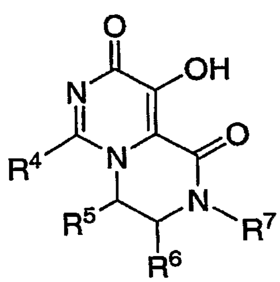
8. The compound according to claim 1, or a pharmaceutically acceptable salt

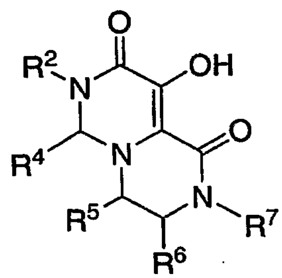
thereof, which is a compound of Formula IIa or IIb:


(IIa)


(IIb).

9. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of Formula IIIa or IIIb:


(IIIa)


(IIIb).

10. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is a compound selected from the group consisting of:

2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

6-acetyl-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-7-pyridin-3-yl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

7-acetyl-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-7-(1-hydroxyethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-7-(1-morpholin-4-ylethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

N-{1-[2-(4-fluorobenzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazin-7-yl]ethyl}-N-methylacetamide;

N-{1-[2-(4-fluorobenzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazin-7-yl]ethyl}-N-methylmethanesulfonamide;

2-(4-fluorobenzyl)-9-hydroxy-7-(1-pyrrolidin-1-ylethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

N-{1-[2-(4-fluorobenzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazin-7-yl]ethyl}-N,N',N'-trimethylethanediamide;

2-(4-fluorobenzyl)-9-hydroxy-7-[1-(methylamino)ethyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

7-bromo-2-(4-fluorobenzyl)-9-hydroxy-6-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

7-[1-(dimethylamino)ethyl]-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-7-{1-[(pyridin-2-ylmethyl)amino]ethyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-7-{1-[(2-methoxyethyl)amino]ethyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-7-[1-(isopropylamino)ethyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-7-{1-[(pyridin-3-ylmethyl)amino]ethyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-6-methyl-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-6-(morpholin-4-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-6-[(methylamino)methyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-6-(piperidin-1-ylmethyl)-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione;

6-[(dimethylamino)methyl]-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-6-methyl-3,4,6,7-tetrahydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione;

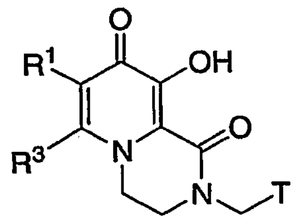
2-(4-fluorobenzyl)-9-hydroxy-6-methyl-7-(1-morpholin-4-ylethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-6-methyl-7-(1-pyrrolidin-1-ylethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-fluorobenzyl)-9-hydroxy-6-[1-(methylamino)ethyl]-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione;
6-[1-(dimethylamino)ethyl]-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,8-dione; and

N-{[2-(4-fluorobenzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrazino[1,2-c]pyrimidin-6-yl]methyl}-N-methylacetamide.

11. A compound of Formula IV, or a pharmaceutically acceptable salt thereof:



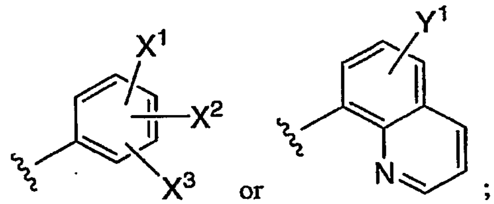
(IV)

wherein R^1 is:

(1) H,
(2) C_{1-3} alkyl,
(3) chloro,
(4) bromo,
(5) CH_2-$N(R^a)R^b$,
(6) $CH(CH_3)$-$N(R^a)R^b$,
(7) CH_2-$N(R^a)$-$C(=O)$-R^b,
(8) $CH(CH_3)$-$N(R^a)$-$C(=O)$-R^b,
(9) CH_2-$N(R^a)$-SO_2R^b,
(10) $CH(CH_3)$-$N(R^a)$-SO_2R^b,
(11) CH_2-$N(R^a)$-C_{1-3} alkylene-O-C_{1-3} alkyl,
(12) $CH(CH_3)$-$N(R^a)$-C_{1-3} alkylene-O-C_{1-3} alkyl,
(13) CH_2-$N(R^a)$-$C(=O)$-$C(=O)$-$N(R^a)R^b$,
(14) $CH(CH_3)$-$N(R^a)$-$C(=O)$-$C(=O)$-$N(R^a)R^b$,
(15) CH_2-OH,
(16) $CH(CH_3)$-OH,
(17) CH_2-HetD,
(18) $CH(CH_3)$-HetD,
(19) CH_2-$N(R^a)$-CH_2-HetA,
(20) $CH(CH_3)$-$N(R^a)$-CH_2-HetA,
(21) HetA, or
(22) $C(=O)$-R^a; and

R^3 is H, C_{1-3} alkyl, or $C(=O)$-C_{1-3} alkyl;

T is



wherein X^1, X^2 and X^3 are each independently selected from the group consisting of -H, halo, $-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, $-C_{1-4}$ fluoroalkyl, $-SO_2-C_{1-4}$ alkyl, $-C(=O)-NH(-C_{1-4}$ alkyl), $-C(=O)-N(-C_{1-4}$ alkyl$)_2$, and HetC;

Y^1 is -H, halo, $-C_{1-4}$ alkyl, or $-C_{1-4}$ fluoroalkyl;

HetA is a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 3 heteroatoms independently selected from zero to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is (i) optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-3}$ alkyl and (ii) optionally substituted with phenyl or $-CH_2$-phenyl;

each HetC is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently a $-C_{1-3}$ alkyl;

HetD is a 5- or 6-membered saturated heterocyclic ring containing a total of from 1 to 3 heteroatoms independently selected from 1 to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms, wherein any ring S atom is optionally oxidized to SO or SO_2, and wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring, and wherein the heterocyclic ring is optionally substituted with $-C_{1-3}$ alkyl;

each R^a is independently H or C_{1-3} alkyl; and

R^b is H or C_{1-3} alkyl.

12. A compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein R^1 is:

(1) H,

(2) CH_3,

(3) bromo,

(4) $CH(CH_3)$-$N(R^a)R^b$,

(5) $CH(CH_3)$-$N(R^a)$-$C(=O)$-R^b,

(6) $CH(CH_3)$-$N(R^a)$-SO_2R^b,

(7) $CH(CH_3)$-$N(R^a)$-$C_{1\text{-}3}$ alkylene-O-$C_{1\text{-}3}$ alkyl,

(8) $CH(CH_3)$-$N(R^a)$-$C(=O)$-$C(=O)$-$N(R^a)R^b$,

(9) $CH(CH_3)$-OH,

(10) $CH(CH_3)$-HetD,

(11) $CH(CH_3)$-$N(R^a)$-CH_2-HetA,

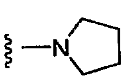
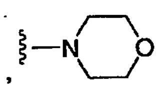
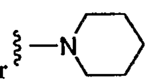
(12) HetA, or

(13) $C(=O)CH_3$; and

R^3 is H, CH_3, or $C(=O)$-CH_3;

T is 4-fluorophenyl;

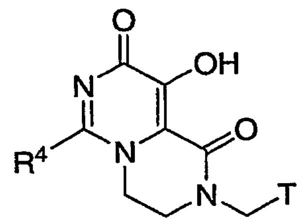
HetA is pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, or pyrazinyl;

HetD is , , or ;

R^a is H or CH_3; and

R^b is CH_3 or $CH(CH_3)_2$.

13. A compound of Formula V, or a pharmaceutically acceptable salt thereof:



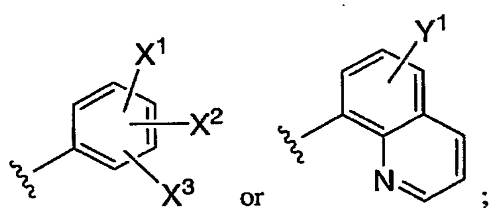
(V)

wherein:

R^4 is:

(1) H,
(2) C_{1-3} alkyl,
(3) CH_2-N(R^a)R^b,
(4) CH(CH_3)-N(R^a)R^b,
(5) CH_2-N(R^a)-C(=O)-R^b,
(6) CH(CH_3)-N(R^a)-C(=O)-R^b,
(7) CH_2-HetD, or
(8) CH(CH_3)-HetD;

T is



wherein X^1, X^2 and X^3 are each independently selected from the group consisting of -H, halo, -C_{1-4} alkyl, -O-C_{1-4} alkyl, -C_{1-4} fluoroalkyl, -SO_2-C_{1-4} alkyl, -C(=O)-NH(-C_{1-4} alkyl), -C(=O)-N(-C_{1-4} alkyl)$_2$, and HetC;

Y^1 is -H, halo, -C_{1-4} alkyl, or -C_{1-4} fluoroalkyl;

each HetC is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently a -C_{1-3} alkyl;

HetD is a 5- or 6-membered saturated heterocyclic ring containing a total of from 1 to 3 heteroatoms independently selected from 1 to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms, wherein any ring S atom is optionally oxidized to SO or SO_2, and wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring, and wherein the heterocyclic ring is optionally substituted with $-C_{1-3}$ alkyl;

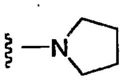
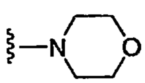
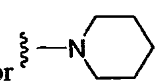
R^a is H or C_{1-3} alkyl; and

R^b is H or C_{1-3} alkyl.

14. A compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) H,
(2) C_{1-3} alkyl,
(3) CH_2-N(R^a)R^b,
(4) $CH(CH_3)$-N(R^a)R^b,
(5) CH_2-N(R^a)-C(=O)-R^b,
(6) $CH(CH_3)$-N(R^a)-C(=O)-R^b,
(7) CH_2-HetD, or
(8) $CH(CH_3)$-HetD;

T is 4-fluorophenyl;

HetD is , , or ;

R^a is H or CH_3; and

R^b is CH_3.

15. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

16. A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof.

17. A method for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof.

18. Use of a compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, for inhibiting HIV integrase in a subject in need thereof.

19. Use of a compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof.

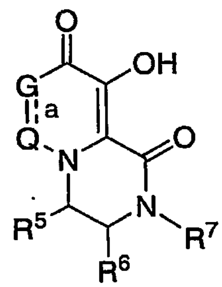
20. A compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for inhibiting HIV integrase in a subject in need thereof.

21. A compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof.

22. A pharmaceutical combination which is (i) a compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, and (ii) an HIV infection/AIDS antiviral agent selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors; wherein the compound of (i) or its pharmaceutically acceptable salt and the HIV infection/AIDS antiviral agent of (ii) are each employed in an amount that renders the combination effective for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS.

ABSTRACT OF THE DISCLOSURE

Bicyclic pyridopyrazine- and pyrimidopyrazine-dione compounds are inhibitors of HIV integrase and inhibitors of HIV replication. In one embodiment, the dihydroxypyridine carboxamides are of Formula I:



(I)

wherein G, Q, bond a, R^5, R^6 and R^7 are defined herein. The compounds are useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS. The compounds are employed against HIV infection and AIDS as compounds per se or in the form of pharmaceutically acceptable salts. The compounds and their salts can be employed as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines.